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PANEL DISCUSSION ON CHEMOTHERAPY IN THE PALLIATIVE TREATMENT OF CANCER*

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MODERATOR JOSEPH H. BURCHENAL: We are living in an age of chemotherapy. During the past twenty years, most of the bacterial, rickettsial, and protozoal diseases have been brought under control by chemotherapy. In cancer, considerable progress has been made, but at present we have no chemical that will cure any form of cancer. There have been certain advances, however, in the last ten years, and the panelists are here to tell you about the present status of chemotherapy in the palliative treatment of cancer.

One form of chemotherapy will not be included because it is too early to discuss it. That is the use of chemotherapy as an adjunct to surgery in an attempt to cure cancer. That work is being carried out under the aegis of Dr. Cole.

The panelists will state what can be accomplished by chemotherapy, compare chemotherapy with radiation therapy, and indicate when each should be used.

We should like to have questions from the audience, preferably written.

Our first speaker is Dr. Henry D. Diamond.

DR. HENRY D. DIAMOND: I shall discuss *chemotherapy of the lymphomas and chronic lymphocytic leukemia.*

In considering any form of chemotherapy, the question of the classification of disease arises. The classification that we use for lymphomas and leukemia is as

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follows: Class 1 refers to Hodgkin's disease, reticulum-cell sarcoma, or lymphosarcoma that is apparently unicentric in origin, arising in a single node locus, and unassociated with constitutional symptoms. Class 2 (that is, clinical Class 2) refers to the disease that is no longer limited to a single locus, yet the regional involvement is still anatomically localized, as in the mediastinum and the neck, or the mediastinum and the axilla; the disease is confined above the diaphragm or below the diaphragm. There may or may not be constitutional symptoms such as chills, fever, night sweats, itching, weight loss, anemia and weakness. In Class 3, which is obviously the class into which leukemia falls by the time one can make a diagnosis, there is universal or generalized systemic disease, usually with constitutional symptoms.

In Class 1 cases, at least on practical grounds, we do not now use a chemotherapeutic agent. Chemotherapy has its realm among Class 2 and Class 3 cases.

Possibly the oldest of the recent chemical agents is *nitrogen mustard*. It is used in Hodgkin's disease of Class 2 and Class 3. It can be used in chronic lymphocytic leukemia, reticulum-cell sarcoma, and lymphosarcoma. Merck markets it commercially as Mustargen. The intravenous route of administration is one of its drawbacks.

Therapeutically, the total dose of nitrogen mustard is 0.4 mg. per Kg. We used to divide the dose so that 0.1 mg. per Kg. was given daily intravenously for four days. Now, however, when the blood count shows a normal level of white cells, or leukocytosis and a normal platelet level, we do not hesitate to give the entire 0.4 mg. in a single dose. This obviates protracted nausea and vomiting for a period of four days, which is what used to occur with the fractionated dose. Danger of venous thrombosis, and marked gastro-intestinal toxicity are associated with its use. From 80 to 90 per cent of patients have nausea or vomiting an hour or longer after administration of the drug. It also suppresses bone marrow activity.

We are not certain how this agent works. It is a general cell poison, but it is radiomimetic, and unique in that particular quality. The patient receiving it should be in Class 2 or Class 3 clinically. Nitrogen mustard is useful in special instances such as in the syndromes of superior vena caval obstruction and spinal cord compression.

Because of the drawbacks inherent in the intravenous administration of nitrogen mustard, an attempt was made to find an agent with similar pharmacologic and therapeutic properties that could be given by mouth. *Triethylene melamine (TEM)* is such a drug. Recalling its formula, there is an ethylene-imine linkage in three places in the triethylene melamine moiety. Thus, it could be predicted from a chemical standpoint that this compound would have properties similar to those of nitrogen mustard, since the active component of HN2 is the ethylene-imine ring.

Triethylene melamine is usually given orally, but it can also be given intravenously. Its indications are identical with those for nitrogen mustard, but benefit is derived from the fact that the patient can be treated while ambulatory. The dosage intravenously is on the basis of 0.04 mg. per Kg. daily for three or four

doses, the total dose usually ranging from 8 to 12 mg. (0.12 mg. per Kg.). Orally, no more than 10 mg. should be given in one week in cases of Hodgkin's disease or reticulum-cell sarcoma. In cases of lymphosarcoma or chronic lymphocytic leukemia, one must be more hesitant and give smaller doses—not more than 5 mg. in one week—because the leukocytes in these instances are extremely sensitive to this drug.

We give triethylene melamine orally the first thing in the morning to the fasting patient, who is allowed water only; breakfast is served one hour later. The dose is 2.5 mg., or half a tablet. Its toxicity is similar to that of nitrogen mustard, though nausea occurs somewhat less frequently. Its mechanism of action, whatever it is, is also similar to that of nitrogen mustard.

Patients are selected for treatment with triethylene melamine on the same basis as for treatment with nitrogen mustard, but include those who are ambulatory.

Among the newer polyfunctional alkylating compounds is *chlorambucil* (CB1348) a phenyl butyric mustard, first given to us by the British—Dalton and others. This agent allegedly has most effect upon the lymphocytic elements of the bone marrow rather than the granulocytic precursors, and perhaps somewhat less effect on the megakaryocytes. Experience has shown, however, that in protracted treatment not only will thrombocytopenia occur with these agents I have mentioned, but granulocytic depression as well.

Chlorambucil can be used in the treatment of certain diseases such as reticulum-cell sarcoma, but perhaps not with the success of nitrogen mustard or TEM. It acts similarly to nitrogen mustard and TEM in Hodgkin's disease, lymphosarcoma and chronic lymphocytic leukemia. However, it becomes effective by a process of accumulation; there is no such acute effect as that obtained with HN2 or TEM. The usual time required for its action to become apparent is two to three weeks from the inception of treatment. When possible, we give a dose of 0.2 mg. per Kg., but at times the dose has to be cut to 0.1 mg. per Kg. It is probably wise to keep it at 0.1 mg. initially in chronic lymphocytic leukemia and lymphosarcoma for the reasons mentioned when discussing TEM and HN2.

Two other new substances are E39 and Sarcolysin.

In the development of these various agents, the parent compound was sulphur mustard, from which evolved nitrogen mustard. Next came triethylene melamine with a similar structure. Triethylene phosphoramide and triethylene thiophosphoramide, which are essentially polyfunctional alkylating compounds, have similar effects upon the lymphomas and chronic lymphocytic leukemia, but we do not use them regularly at present in our institution in the treatment of lymphomas. Bateman has remarked that they may be effective in breast cancer.

Myleran is another alkylating compound of interest. It seems to act upon granulocytic elements. Dr. Ellison probably will tell us more about its effect upon granulocytic leukemia. In a recent study at the Institute, we found that Myleran can restrict Hodgkin's disease and lymphosarcoma in some patients, if it is given long enough.

6-Mercaptopurine probably has little place in the treatment of malignant

lymphomas, although, occasionally, a patient with Hodgkin's disease or lymphosarcoma will show some response.

Adrenocortical steroids (*e.g., prednisone, prednisolone*), *ACTH*, and some even newer compounds apparently have a lympholytic effect as well as a nonspecific effect upon patients with Hodgkin's disease, lymphosarcoma and reticulum-cell sarcoma. There is little evidence to date that the tumor of Hodgkin's disease is in any way lysed by these agents, whereas lympholysis does occur in lymphosarcoma, chronic lymphocytic leukemia, and some reticulum-cell sarcomas. The toxicity and mechanism of action are well known.

In summary, the polyfunctional alkylating compounds (nitrogen mustard and its cousins), adrenocortical steroids and ACTH are the compounds useful in the treatment of malignant lymphomas and chronic lymphocytic leukemia. Occasionally, even such agents as Myleran and 6-mercaptopurine may exert a transient, evanescent effect upon malignant lymphomas.

Let us not forget that there are other forms of treatment, primarily radiation therapy, for these diseases. At times these other forms are better, and at times not as good as chemotherapy.

Selection of the patient is the paramount consideration, in terms of the results of treatment. If there are constitutional symptoms, that is, generalized systemic disease, chemotherapy will treat the patient as a whole. If the tumors are bulky, radiation therapy will do a better job in terms of the individual tumor. At other times, as in the vena cava syndrome and incipient paraplegia, the chemotherapeutic agents are indispensable.

MODERATOR BURCHENAL: Dr. Rose Ruth Ellison will discuss *acute leukemia and chronic granulocytic leukemia.*

DR. ROSE RUTH ELLISON: Chronic leukemia is frequently seen in older people, but acute leukemia is often thought to occur primarily in children. However, it recently has been shown that acute leukemia, which has a peak incidence (per million population) below the age of 10 years, has an incidence in older persons at least as high as that seen in children. From 40 to 50 per cent of all cases of acute leukemia occur in persons over the age of 15 years. In this group, the disease seems to be somewhat different. Morphologically, there is a greater percentage of myelocytic or monocytic leukemia among older persons.

Occasionally, a patient with acute leukemia may live for as long as a year and a half, without specific therapy or without a response to specific therapy. However, the survival time in adults with acute leukemia is similar to that in children, the median being six to six and a half months.

Our aim in the treatment of acute leukemia is the production of a remission. When a complete remission occurs, the bone marrow returns to normal, the peripheral blood returns to normal, and there is clearing of all physical signs and symptoms of the disease. Unfortunately, this favorable result is transient. Usually, if there is any response in adults, it is only a partial one. These partial responses are frequently as useful clinically in improving the patient as are complete responses. Here, too, the disease differs from that seen in children in that the incidence of responses is much smaller.

The two main groups of agents available for treatment are the *adrenocortical*

steroids and antimetabolites. The adrenocortical steroids are useful in acute situations, *i.e.*, when a patient is bleeding severely, has a high fever, and is acutely ill. Beyond the age of 30 years, the occurrence of a remission with the use of adrenal steroids is extremely rare. They are of value in the treatment of hemorrhage, but the platelet count rarely rises and the bone marrow rarely returns to normal. We have found prednisone to be quite useful, because hypertension and sodium retention are avoided. Hypercalcemia and, occasionally, mental changes have been problems.

When a remission is induced by an antimetabolite, it is usually more lasting. Again, the responses in adults are much poorer than in children. The purine antagonists, 6-mercaptopurine and 6-chloropurine, are the best agents available at present for treating adults, since there is some chance of a response.

The folic-acid antagonists are of little value in adults. We do not give them initially because of the poor chance of remission.

The glutamine antagonists, azaserine and DON, have not proved useful by themselves in either children or adults. The responses, if any, are transient and partial. In children, however, the combination of azaserine with 6-mercaptopurine seems to alter the duration of remissions, but probably has not increased the incidence. We have not seen such an effect in adults.

With any antimetabolite, it takes at least three weeks before a response is evident. Thus, patients may need support during the first few weeks of therapy. When using 6-mercaptopurine, eight weeks may be necessary. We have seen responses occur as late as seventeen weeks after the beginning of treatment. In adults, the average duration of therapy required to produce a remission is seven or eight weeks, although a decrease in the leukocyte count and some clinical change may occur earlier.

We use 6-mercaptopurine in a dosage of 2.5 mg. per Kg. daily, and give this continuously, stopping only if the leukocyte count is falling rapidly.

In the patient with a low leukocyte count initially and a cellular or hypercellular bone marrow, we do not worry about the presence of leukopenia. If normal cells appear, the leukocyte count tends to rise towards the normal range while the drug is being continued, so that leukopenia is not a problem. Thrombocytopenia occurs in most of these patients prior to therapy and is not a contraindication to the use of antimetabolites. If a remission occurs during treatment, the platelet count rises to the normal range despite continued therapy.

Once a remission is attained, 6-mercaptopurine should be continued at the full dosage of 2.5 mg. per Kg. daily. Relapse occurs rapidly when treatment is stopped—usually within four to six weeks.

Intermittent therapy can be used, but there are the associated problem of ups and downs in the clinical course, as well as the fact that, again, three weeks may be necessary to obtain a second response.

Aside from the hematologic depression, the only other noteworthy manifestation of toxicity is the occasional occurrence of nausea and vomiting. This happens in about one-quarter of the adults who receive the drug. It usually is not severe enough to necessitate stopping treatment.

One-quarter to one-third of the adults we have treated with 6-mercaptopurine

or 6-chloropurine have responded with a complete or partial remission. Among those treated for at least three weeks, there was a much larger percentage of responses, as this period eliminated patients who were extremely ill and died of their disease within the first few weeks of therapy. There is a difference in response, even among adults, depending upon age. In patients aged 40 years or over, the response rate is about half that in patients between the ages of 15 and 40 years.

Although folic-acid antagonists are usually not of much value in adults, there is some indication that once a patient has responded to 6-mercaptopurine and then becomes resistant to it, he may respond to the folic-acid antagonists. We have been using this form of therapy recently, on an experimental basis.

Dr. Diamond mentioned the importance of *radiation therapy* as in the treatment of chronic lymphatic leukemia. It usually is not used in acute leukemia, but situations occasionally arise in which it is necessary.

When the tumors are bulky and are causing symptoms, radiation therapy in small doses is effective. An illustrative case is that of a man with acute leukemia who experienced a remission of the disease and regression of mediastinal adenopathy while receiving 6-mercaptopurine. Subsequently, he became resistant to this drug. He then responded to cortisone, and again there was a favorable change in the chest roentgenogram. Thereafter, without development of a hematologic relapse, there was widening of the mediastinum associated with cough and dyspnea. Radiation therapy to this area produced another regression.

Radiation therapy is also useful in cases of acute leukemia with paraplegia or with brain symptoms. Sometimes pain in the joints is a problem in these patients, and small doses of radiation applied to the area involved are beneficial.

Despite all of the forms of treatment available, we have not effected much change in the survival time of adults with acute leukemia. Prior to the use of folic-acid antagonists, purine antagonists and adrenal steroids, the median survival time in children with acute leukemia was about five months. At present, with the use of all available agents, the survival time in 50 per cent of the children has been increased to just over twelve months. In adults, however, there has been no change in survival time. This does not mean lack of response, but probably indicates that the number of responses is too few to affect survival time.

Among patients with either a complete or partial remission, those who responded to 6-mercaptopurine had a median survival time of ten months, and those who responded to 6-chloropurine had a median survival time of thirteen and a half months. This is not a matter of weeding out the most severe cases, since patients who received these drugs for at least three weeks and experienced no remission did not have similar prolongation of the median survival time.

Admittedly, we have not progressed far, but the forms of therapy now available do seem to have prolonged the survival period in the patients who respond.

Several agents can be used for the treatment of chronic granulocytic leukemia; the selection depends upon the stage of the disease. When the patient is first seen, there usually are symptoms. Unlike chronic lymphocytic leukemia, which may continue for years without the need for treatment, chronic granulocytic leukemia usually requires treatment immediately.

Early in the disease, the abnormal findings are responsive to a number of agents. Radiation therapy to the spleen is a standard method and is very beneficial. The nitrogen mustard analogs (such as triethylene melamine, triethylene phosphoramide, triethylene thiophosphoramide or Myleran) are effective. Radioactive phosphorus (P^{32}), Fowler's solution, and urethane also produce improvement. 6-Mercaptopurine is useful early in the disease. The improvement that occurs with any of these agents consists of a decrease in the leukocyte count, an increase in hemoglobin to normal levels, and a decrease in the size of the spleen.

As the disease progresses, management becomes more difficult, in that larger doses of radiation or of the nitrogen mustard analogs may be necessary. Gradually thrombocytopenia becomes a problem as the disease becomes more severe, associated with fever, increased anemia, and lympadenopathy. Thrombocytopenia is a limiting factor in the use of most of the usual agents, *e.g.*, mustard analogs, Fowler's solution and urethane. In fact, administration of these compounds may aggravate bleeding at this time. The adrenocortical steroids may decrease the bleeding tendency, but usually they do not cause any real change in the disease picture.

In this acute phase of chronic granulocytic leukemia, 6-mercaptopurine is occasionally of value in obtaining a transient remission. It is used in the same way as in acute leukemia.

Myleran is probably one of the most useful agents. It can be administered over a prolonged period. At the start of therapy, the leukocyte count must be watched fairly closely, since patients vary in sensitivity. The recommended initial dosage is 4 to 6 mg. daily. Once the leukocyte count has reached normal levels during the first course of therapy, it is well to stop treatment for a while, since some patients may continue to have normal counts and be in good condition for prolonged periods. However, most patients require maintenance therapy with Myleran in a dosage of about 2 mg. daily. The only way to determine the maintenance dosage is to test the individual patient.

Thrombocytopenia is not usually a problem with Myleran, but it can occur. The patient must be watched, as thrombocytopenia can develop without excessive lowering of the leukocyte count below 4000 or 5000 per cu. mm. Unlike the mustard analogues, Myleran rarely causes nausea and vomiting.

The median total duration of chronic granulocytic leukemia does not appear to have been altered significantly by any of the present chemotherapeutic agents or by irradiation therapy as usually given. The only report of prolongation of the course of chronic granulocytic leukemia concerns the use of frequent small titrated doses of radioactive phosphorus, the treatment being given at regular intervals whether the disease is in relapse or in remission.

With any of these modes of therapy, the patient leads a much more comfortable and useful life. Treatment should be given despite the fact that the prognosis is poor and the over-all duration of the disease is known in advance.

MODERATOR BURCHENAL: Dr. George Escher will discuss *the treatment of malignant disease of the breast and prostate.*

DR. GEORGE C. ESCHER: The effect of *hormone therapy* upon tumors has been

known longer than the effect of chemotherapy. As long ago as 1896, Beatson reported on the efficacy of castration in advanced breast carcinoma. However, the major impetus in this field had to await the availability of larger amounts, purer types, and cheaper sources of the hormones currently used in the treatment of some of the solid tumors.

I shall try to give a short presentation of the present management of carcinoma of the breast and prostate. In general, *castration* is the first choice of treatment of advanced prostatic carcinoma. The administration of hormones is more effective following castration. The combination of castration and estrogen therapy has given excellent results in carcinoma of the prostate; the responses can be both dramatic and protracted. Many of us can recall patients in whom the disease was well controlled by castration for as long as five to seven years, who subsequently showed a symptomatic response to estrogen. Improvement in the serum acid phosphatase level has been associated with the use of stilbestrol.

The dosage of stilbestrol in general use is from 0.5 to 1 mg. a day. Other estrogens are similarly effective in comparative dosages. In carcinoma of the prostate, favorable objective responses to hormone therapy vary between 50 and 70 per cent. In carcinoma of the breast, on the other hand, the maximum is 20 to 30 per cent (castration excepted).

Recently, a question arose in the minds of several urologists as to how good estrogens really are in the treatment of prostatic cancer. I understand that a double-blind study may soon be instituted for the testing of estrogen against lactose. This indicates that no one is satisfied with present results and is trying to make sure that he chooses the best therapy. It will be interesting to see what information is derived from this particular study.

Adrenalectomy has largely been abandoned in the treatment of genital carcinoma. Most of us think that it has no great value.

Hypophysectomy has been performed in a small series of cases, with mixed results. It is not universally recommended.

In our own series of 200 androgen-treated patients with carcinoma of the breast (unselected prior to treatment) we obtained an objective response rate of about 20 per cent. Subjective response occurs much more frequently, even in the presence of progression of disease, and can be misleading. We rigidly define objective response. If there are multiple lesions, none of which shows progression, it is necessary that at least one lesion show regression, before the response can be classified as an objective one.

There was a response to estrogen in about 27 per cent of our cases of breast carcinoma. We have definite criteria about when to use estrogen and when to use androgen. Ten years postmenopausal is the dividing line for the use of androgen as opposed to estrogen, estrogen being used after that period. The Committee on Research of the American Medical Association originally recommended five years postmenopausal as the dividing line. We prefer to be more conservative in that respect.

It has been strongly recommended that castration be the first step in therapy in any woman with breast carcinoma less than one year postmenopausal and

with sufficient ovarian activity. Although I quoted figures of 20 to 30 per cent response to hormone therapy, castration is the exception. With castration, beneficial results are obtained in about 40 per cent of the cases. Therefore, we strongly urge that this be the first procedure in the young woman.

Next is the matter of lesion response. A doctor may call you and say, "I have a patient with lung metastasis from breast cancer. She is a young woman. I read in the literature that I should use estrogen for soft-tissue diseases. What about androgen?" The point is that estrogen can elicit a response not only in soft tissue, for which it was originally recommended several years ago, but also in the bone lesions.

Adrenalectomy and hypophysectomy are additional ablative procedures which are of limited value, particularly in patients who have shown a response to castration. Hypophysectomy is currently preferred over adrenalectomy. These procedures are not recommended when castration has failed.

Patients with breast cancer vary with reference to the area of metastatic involvement, *e.g.*, some have predominantly osseous lesions, some have predominantly cutaneous and lymph node lesions, and some have predominantly visceral lesions (brain, liver, lung). The last group has the shortest survival time regardless of treatment. Liver metastasis is reported to be a contraindication for adrenalectomy or hypophysectomy and brain metastasis has been reported as a contraindication for hypophysectomy.

I do not imply that adrenalectomy and hypophysectomy are not useful procedures. They are definitely useful, but one must study the statistics carefully and see that there is selection of patients. When one adjusts the selected adrenalectomy and hypophysectomy series for proper comparison with the non-selected series of patients treated with hormones, it will be found that the number of objective responses in these 2 groups are similar, *i.e.*, between 20 and 30 per cent.

Dr. David A. Karnofsky: My assignment is to discuss *the use of chemotherapeutic agents in nonresectable or far-advanced carcinoma.*

This group includes about 75 per cent of all neoplasms; that is, in addition to the breast and prostatic carcinomas which Dr. Escher discussed.

It is necessary briefly to review some of the information already given to you with regard to the drugs available. First is *nitrogen mustard.* The usual dose is 0.1 mg. per Kg. of body weight daily for four days, but in many cases, as Dr. Diamond mentioned, it is possible to give the entire treatment in a single injection of 0.4 mg. per Kg. This is feasible particularly in cases of carcinoma without bone marrow involvement.

There is no need to provide a list of the various *relatives of nitrogen mustard,* such as TEM, chlorambucil, Thio-TEPA, and Myleran—a group which has been called the polyfunctional alkylating agents. It should be emphasized that, as far as we know, these drugs have a similar effect in equivalent biologic doses on the various carcinomas for which they have been tried.

The second category of drugs comprises the *antimetabolites,* which may have special effects in certain types of carcinoma. One of the most important is the *folic-acid antagonist,* amethopterin. This drug interferes with the activity of folic

acid, an important vitamin. The usual dosage in the adult is 5 mg. a day. In some clinics, rather than give this dose over a long period of time, massive doses (25 or even 50 mg. per day) have been given intravenously or intramuscularly. For most purposes, a dosage of 5 mg. a day is used, with careful observation of the patient in relation to the level of toleration. This drug can be extremely toxic; it may cause lesions of the intestinal tract, depression of the bone marrow and hemorrhagic diathesis.

A third group of drugs (also antimetabolites) comprises the *glutamine antagonists*, DON and azaserine. They will be discussed in more detail by Dr. Myers. Generally speaking, they have had a profound effect on the growth of transplantable cancer in animals and have been studied intensively in human beings by both Dr. Ellison and Dr. Magill. We have no convincing evidence that they play an important role in the clinical management of cancer, but they have some special effects which may prove useful under certain conditions.

We should note these drugs particularly, because in the future they may prove to be indicated in certain situations. They can be given by mouth, intravenously, or intramuscularly. The usual dose of DON, the one most generally used, is 0.2 to 0.3 mg. per Kg. of body weight daily. Its action is similar to that of azaserine.

The principal toxic manifestation is oral lesions. If the dose is continued, severe gastro-intestinal symptoms and depression of the bone marrow may occur.

Another form of treatment for carcinoma is one of the *adrenocortical hormones*. We generally use prednisone.

I should like next to review the specific situations wherein one or the other of these drugs may play a useful role.

One of the most striking effects produced by a chemotherapeutic agent is that of nitrogen mustard on *lung cancer*. In order to put the use of these drugs in proper context in regard to management of the patient, it should be emphasized that surgery is the first form of treatment if the lesion is resectable. If the lesion is nonresectable but localized, a more profound effect upon the tumor can be obtained by the use of localized radiotherapy. On the other hand, in some cases of generalized disease—with widespread pulmonary involvement, or with superior vena cava compression syndrome—nitrogen mustard may cause prompt relief of symptoms. Local radiotherapy can then be given, if indicated. In patients who are not responding to radiotherapy, or who are not considered suitable for this form of treatment, a trial of nitrogen mustard or a related compound may sometimes provide considerable symptomatic relief.

Among 35 patients with lung cancer whom we studied in detail, administration of nitrogen mustard brought about objective regression of the disease in 40 per cent (*i.e.*, the tumor shrank, though the disease did not disappear). Complete symptomatic relief occurred in 20 to 30 per cent of the patients. In 67 per cent of the group who presented the syndrome of superior vena cava compression, nitrogen mustard produced prompt improvement. In about 40 per cent of the patients there was partial relief of pain, and in 30 to 40 per cent there was no benefit. Thus nitrogen mustard is an effective agent for producing temporary improvement.

The remissions induced by nitrogen mustard are fairly brief, averaging three to six weeks. One can repeat the treatment, but the response, even though excellent at first, becomes less satisfactory with repeated courses.

Some patients, after responding to nitrogen mustard, have been maintained on TEM with satisfactory symptomatic improvement for several months or longer. However, nitrogen mustard or the alkylating agents have not been important factors in prolonging life in patients with lung cancer.

To recapitulate, the indications for the use of nitrogen mustard in lung cancer are: 1) the presence of the superior vena cava compression syndrome (HN_2 is the initial form of treatment, followed by local radiation); 2) widespread cancer; 3) cases no longer suitable for radiation therapy; and 4) recurrent pleural effusion (which I shall refer to later).

A second type of neoplasm that responds to alkylating compounds (including nitrogen mustard, TEM and Thio-TEPA) is *ovarian cancer*. In order to place this form of therapy in its proper context it is necessary to emphasize that surgical excision, when possible, is the first treatment indicated in ovarian cancer. In the patient with recurrent disease or a nonresectable lesion, we usually recommend prophylactic radiotherapy immediately after the operation, with tumor doses of 3,000 to 4,000 r. Hormone therapy has, in general, not been effective in ovarian cancer.

In our institution, when treating cases of recurrence with abdominal masses or ascites, we use intravenous and oral TEM. In 40 per cent of these patients, there has been definite symptomatic improvement with resolution of ascites and clearing of intestinal obstruction. These responses last from one to three months. The patient who responds to triethylene melamine can be maintained with oral TEM, sometimes for a year or longer. We therefore, regard the alkylating compounds—either nitrogen mustard by intravenous injection, TEM intravenously or orally, or Thio-TEPA—as useful agents in the treatment of advanced ovarian cancer.

As Dr. Escher pointed out, alkylating compounds have been used in *mammary cancer*, but in our experience they have not been particularly effective in far-advanced disease. Less than 10 per cent of our patients with advanced breast cancer obtained substantial improvement with Thio-TEPA, TEM, or nitrogen mustard. Without question, these were cases of advanced disease. By the time an alkylating agent is used, the patients may have had hormonal therapy for a year or more, while the disease was progressing. The use of alkylating compounds represents a last-ditch effort.

Other clinics commence the use of Thio-TEPA earlier in the clinical course of the disease. This may explain partially the discrepancies between the poor results we have obtained and the better results reported from other institutions.

Another type of carcinoma responsive to specific agents is that of the thyroid. Generally speaking, about 50 per cent of *thyroid carcinomas* can be made to concentrate radioactive iodine. However, the concentration achieved is usually not high enough to have an important effect upon the disease. Only from 5 to 10 per cent of all thyroid cancers are significantly benefited by radioactive iodine. How-

ever, it is a useful form of treatment in cases of metastatic thyroid cancer that show a high uptake of I^{131}.

Another specialized situation is *chorio-epithelioma* in the female. This tumor is frequently malignant and metastatic. It can be controlled in several ways, which suggests that it is a responsive type of tumor. Nitrogen mustard can cause regression in chorio-epithelioma; in 1 case, a patient has remained apparently cured of pulmonary metastases after five years.

Drs. Li and Hertz, at the National Institutes of Health, have reported on the use of amethopterin in the treatment of chorio-epithelioma; metastatic disease apparently has been controlled by treatment for prolonged periods, and possibly cures have been achieved. Probably not more than 200 cases of chorio-epithelioma occur in the United States each year, so it is a rare form of cancer.

The physician interested in cancer is confronted with many specialized problems, which I should like to discuss briefly. These may be related to the tumors that I have discussed, or to the many other types.

The management of *central nervous system metastases* often involves the use of a single large dose of nitrogen mustard followed by local radiotherapy to the involved area. Nitrogen mustard frequently produces prompt symptomatic and objective improvement, and the radiation therapy enhances and prolongs the response.

Regarding the *pulmonary dissemination of cancer*, I have already mentioned the use of nitrogen mustard in *carcinoma of the lung*. We have also observed occasional regression of pulmonary metastases for short periods of time (such as seven weeks) in cases of carcinoma of the cervix.

In the patient with *massive pelvic carcinoma*, often with urethral compression and impending uremia, nitrogen mustard may be useful. Dr. Sullivan has developed a simple technic that involves the introduction of a large-bore needle into the femoral artery by direct puncture; a polyethylene catheter is run through it into the abdominal aorta. By this method the pelvic organs can be perfused with nitrogen mustard in a single injection; then the catheter and needle are withdrawn. The treatment can be given in ten to fifteen minutes. Thus one delivers a larger dose of mustard to the tumor-bearing area than to the systemic circulation. Regression has been obtained in cases which probably would not have responded to the intravenous injection of nitrogen mustard.

Hepatic metastases present another major problem. Here, we must confess that we have had little success with chemotherapeutic agents. Administration of DON may possibly delay the progression of these metastases, although it is too early to tell whether or not there is a true effect in comparison with the natural evolution of the disease. Nitrogen mustard may occasionally produce some regression of hepatic metastases. We depend more upon radiation therapy of the liver to relieve symptoms, to alleviate jaundice, and to control the growth of the tumor.

Recurrent ascites may sometimes be controlled with intra-abdominal nitrogen mustard, radioactive gold, or chromic phosphate.

In the treatment of *recurrent pleural effusion*, nitrogen mustard is often effective. Dr. Weisberger, whose results are better than ours, has reported relief of

effusion in about 65 per cent of his patients. We obtained relief in about 25 per cent; generally speaking, the results with mustard and with radioactive gold were similar.

In summary—I have reviewed conditions that do not respond specifically or consistently to chemotherapy. The results are not completely discouraging, and some conditions can be improved to a certain extent.

We advocate an active program of therapy. Under this regimen, the morale of the patient is better, occasional improvement is gratifying, and, in an important sense, advanced cancer is not being accepted passively by the physician. Active treatment goes hand in hand with interest, thought, and study. The management of cancer will be generally improved, if patients with advanced cancer are treated.

In this respect, the aspirations and limitations of the chemotherapist are similar to those of the geriatrician who strives to improve the status of the medical care of the aged without necessarily being able to cure old age.

MODERATOR BURCHENAL: Dr. Laird Myers will discuss *the problems of hypercalcemia in cancer patients.*

DR. W. P. LAIRD MYERS: In an effort to measure changes in tumor growth objectively, Pearson and others have carried out extensive studies on calcium metabolism in cases of osteolytic cancer. They have shown that when cancer invades bone, patients lose calcium and phosphorus in the proportions in which these elements exist in bone.

The disturbed calcium metabolism in malignant disease results in the displacement of calcium from bone in large amounts, with initially an outpouring into the urine. When excretion mechanisms are exceeded, the serum level rises.

If an agent is administered so that either the osteolytic focus stops growing (a carcinostatic effect) or it shrinks (a carcinolytic effect), the release of calcium from bone is reduced, the serum level returns to normal, and the amount excreted in the urine returns to normal.

Problems of disturbed calcium metabolism are not uncommon. We have reviewed 53 cases of hypercalcemia in malignant disease observed during the course of one year. The most common lesions associated with hypercalcemia proved to be those of kidney, lung and breast origin, as well as myeloma and lymphoma.

The presence of hypercalcemia in a great number of breast carcinoma patients is due partly to the fact that there is steroid-induced calcemia in this group.

That changes in calcium metabolism may reflect changes in tumor growth is illustrated by the case of a 62-year-old man with lymphosarcoma. The primary disease affected the cervical region, with bulky lymphadenopathy. The serum levels of alkaline phosphatase and calcium were followed sequentially, as well as the urinary calcium excretion. He was treated with a combination of 6-mercaptopurine and azaserine. There was a steady fall to normal in the concentration of serum calcium, a return to normal of the urinary calcium, and a corresponding rise in the serum level of alkaline phosphatase. These alterations were thought to be evidence of bone repair. At the height of these chemical changes, there was obvious shrinkage of the visible soft-tissue tumor.

It is often pointed out that despite changes in, for example, urinary calcium

in response to therapy, the skeletal situation does not change, *i.e.*, the extent of disease is the same, or else there is no healing. This does not mean that therapy was ineffective. The changes in calcium mean that the rate of tumor growth or function is affected. It either slows down or ceases with therapy, but healing of bone may not necessarily take place. Therefore, the extent of involvement seen upon skeletal survey remains unchanged.

The application of these principles is demonstrated by the case of a 61-year-old woman with metastatic breast carcinoma who was treated with TEM and Thio-TEPA sequentially to the point of leukopenia. The concentration of serum alkaline phosphatase, which had been normal, rose to a distinctly high level. The serum calcium level fell to normal in response to therapy, as did the urinary calcium excretion. This was objective evidence of the effectiveness of these agents.

The problem of hypercalcemia arose in a woman with lymphosarcoma. She was comatose, with a serum calcium level of 20 mg. per 100 ml., and a urinary calcium excretion of 800 mg. per twenty-four hours. There was a prompt change to normal in both of these values following the administration of nitrogen mustard. The effect was short-lived, however. Upon recurrence of the hypercalcemia, cortisone was started and a similar change in calcium metabolism was observed.

Cortisone may be useful in the management of these problems. For instance, a man with osseous metastases secondary to adenocarcinoma (primary site unknown) had elevated levels of serum and urinary calcium. Upon treatment with cortisone, a sequential return of both values to the normal level was observed.

We have utilized this technic in the study of an agent that Dr. Karnofsky mentioned, namely, DON. This compound was tried in a woman with cancer of the breast, metastatic to the skeleton. She had hypercalcemia with a serum level of 17 mg. per 100 ml., and hypercalciuria. The administration of DON resulted in a dramatic fall to normal of both the serum level and urinary output of calcium, and a rise in serum alkaline phosphatase activity. This was evidence that DON had inhibited the rate of growth or function of the metastatic tumor in the skeleton.

DON and 6-mercaptopurine administered simultaneously in breast cancer produce similar changes in serum and urinary calcium.

A noteworthy complication is the *hypercalcemia and hypercalciuria induced by hormone therapy in patients with breast cancer*. The results of serial urinary calcium determinations may give warning. On the basis of the rising excretion of calcium in the urine of patients with breast cancer, we discontinue testosterone therapy at a time when the blood calcium level is still normal, anticipating a delayed rise. When treatment is stopped, the whole process is reversed.

Thus, in the appraisal of chemotherapeutic agents, studies of serum and urinary calcium afford an excellent means of measuring changes in the rate of growth or function of tumors in bone.

MODERATOR BURCHENAL: Thank you, Dr. Myers.

We have a number of questions from the audience. We shall start with a fairly explosive one: "*Will you discuss Krebiozen in the treatment of cancer, putting*

it in proper perspective for practicing physicians?" I shall direct that question to Dr. Karnofsky.

DR. KARNOFSKY: I think everyone has heard of this material. I shall tell briefly what we know about it scientifically.

The material was originated by a man who, as far as I know, has made no contribution to science or to medicine. The drug is a secret one. Its method of preparation has not been described. Its chemical formula is unknown. It seems that none is available in pure form for any kind of testing. There is no evidence that it has any biologic activity in animals, so there is no assay method for it.

The world supply of this material was apparently dissolved in mineral oil, in a concentration of 10 gamma per cubic centimeter, or 1 part in 100,000. It seems almost impossible to detect an unknown material in that large pool of mineral oil.

The original clinical results were obtained under unfavorable conditions; a number of clinics used it, but none of them, to my knowledge, represented a group with experience in the management of cancer. In reviewing the clinical data provided by the people promoting this material, there is no evidence that it has any useful effect upon the course of cancer.

The sole support of this material, scientifically, has been the name of Dr. Ivy, who has devoted his time to it during perhaps the last six years. Despite the fact that Dr. Ivy has in the past reported other investigations in reputable medical journals, the data on Krebiozen have never been presented in a manner that would make it acceptable to scientists or physicians.

Putting it in its proper context as far as the practicing physician is concerned—this is my personal opinion—Krebiozen is a secret remedy, and any doctor who uses it is performing a disservice to his patient and to the dignity of the medical profession.

MODERATOR BURCHENAL: Thank you, Dr. Karnofsky.

This question is directed to Dr. Escher: *"In advanced carcinoma of the breast, do you recommend castration by operation or radiation? Which is more effective and do you always recommend it?"*

DR. ESCHER: Castration, preferably surgical, is recommended in the patient who is less than one year past the menopause, when there is an inoperable mammary carcinoma, either recurrent or primary.

In a comparison of surgical with radiation castration, unfortunately we do not know what constitutes an ovarian suppressive dose of radiation therapy. We can only state that a 600 to 2,000 r depth dose will produce amenorrhea. As there are no reliable methods of measuring endogenous estrogens, we feel somewhat insecure. However, many patients cannot undergo surgery for physical reasons; in these instances we suggest a 1,200 r depth dose delivered in a period of one to two weeks.

MODERATOR BURCHENAL: Thank you, Dr. Escher.

The next question is for Dr. Karnofsky, Dr. Diamond, or Dr. Ellison, whoever wants to answer it: *"Is there any effective treatment for excessive bone marrow depression during therapy? What about vitamin B_{12}?"*

DR. DIAMOND: I know of no specific remedial agent, but I can answer the last part of the question by saying that vitamin B_{12} is of no avail.

We occasionally attempt to tide the situation over by the use of adrenocortical steroids. Whether there is a truly specific effect upon the bone marrow in terms of production of platelets and leukocytes, is open to question. Empirically, the observation has been made that these agents may hasten the return of function of bone marrow.

MODERATOR BURCHENAL: Any further comment?

It might be worthwhile mentioning that the use of homologous bone marrow—that is, from another donor— has been tried in a few patients. It is too soon to know whether it will work or not. From the data pertaining to animals, it would not seem too likely.

Here is a question for Dr. Diamond: "*What are the indications for, and the dangers of, combining radiation therapy with alkylating agents?*"

DR. DIAMOND: That question is extremely simple to answer. The radiotherapist believes that you cannot combine the two because excessive suppression occurs. The chemotherapist is, at times, fearful of the combination. Actually, one can readily use both methods in most cases.

To patients in our clinics and in the hospital, whom we select for combination therapy, we give a complete course of the chemotherapeutic agent (nitrogen mustard, for instance) in a single dose, and begin radiation therapy the same day or the next morning. The peak effects that we see in terms of leukopenia are those related to the nitrogen mustard; they usually disappear within three to five weeks. The peak effect of nitrogen mustard may be acute when a full course is given in a single injection; it may occur about the eighth to tenth day after injection. Yet radiation therapy may be continued and eventually the leukocyte count will return to normal. This is a bugaboo which is not of great consequence.

MODERATOR BURCHENAL: Dr. Escher, I think you covered this: "*Which is more effective in controlling pain in bone metastases—hypophysectomy or adrenalectomy?*"

DR. ESCHER: I would first try additive hormones. Actually, the question is more than that: "*Which is the easier case to manage?*" Most of us believe that the post-hypophysectomy case is somewhat easier to handle.

MODERATOR BURCHENAL: Here is a hypothetical question for Dr. Ellison: "*As a rule, malignant diseases in patients during the last decade of life progress more slowly than similar diseases during the first decade of life. Why does this not hold true for the leukemias?*"

DR. ELLISON: I do not know why it does not hold true. Recently, a survey was made by Gunz of patients over the age of 50 with acute leukemia. This was published in *Blood*. He thought that, despite the length of time patients might have had symptoms prior to diagnosis, once they became ill enough to seek medical care they went downhill just as rapidly as did children.

We have observed this also; yet in an occasional patient the disease may continue for a year or a year and a half without response to treatment. Many of the older adults with acute leukemia exhibit the same pattern of symptoms and rapid downhill course seen in children.

MODERATOR BURCHENAL: In line with this question—in chronic leukemia (chronic lymphocytic leukemia, particularly) the elderly patient is more likely to have slowly progressing disease than is the patient aged 40 to 50. Would you agree with that, Dr. Diamond?

DR. DIAMOND: In general, yes.

DR. ELLISON: When chronic granulocytic leukemia occurs in children, it represents the same process as in the older adult.

MODERATOR BURCHENAL: Dr. Escher: "*Have you applied combined androgen and estrogen therapy in breast cancer, and with what results?*"

DR. ESCHER: I have not, because, based on our data on the behavior of a tumor, the lesion might at one and the same time respond to one hormone and be severely exacerbated by the antagonistic compound. We might be working both ends against the middle and encounter difficulty.

MODERATOR BURCHENAL: Here is another question for you, Dr. Escher: "*What is your opinion of the routine use of combined androgen and estrogen therapy in small doses in all geriatric patients, for the purpose of delaying the aging process? Is there any danger of hastening the development of malignant disease in these patients?*"

DR. ESCHER: No one has at any time been able to prove that the use of estrogens in the postmenopausal female or the use of estrogen-androgen combinations for, say, osteoporosis in the aged, has induced carcinoma.

Some of us think that there has been excessive use of estrogen-androgen combinations. This is why many cautionary remarks have been published in the literature. However, I still think my first statement holds true. No one has proved this danger in the human being. I use these agents sparingly.

MODERATOR BURCHENAL: Dr. Karnofsky: "*What do you use to prevent or treat the nausea and vomiting accompanying chemotherapy?*"

DR. KARNOFSKY: The only chemotherapy this would refer to is nitrogen mustard. If this compound is to be given intravenously, we usually give it in the late afternoon or evening. Within ten minutes after the injection, we give 100 mg. of sodium luminal and 25 mg. of chlorpromazine, and repeat this in two or three hours, if vomiting is severe. However, some patients do not vomit at all, or very little, and the anti-emetic treatment may be more disturbing than an episode of nausea and vomiting, in that the patient may feel drowsy for the next day or so.

MODERATOR BURCHENAL: Dr. Diamond, or anyone else on the panel who cares to talk on this: "*Do you consider polycythemia vera among the possible malignant diseases? Please comment on the advisability of using radioactive phosphorus (with or without preliminary venesection to reduce blood volume) in the treatment of polycythemia vera.*"

DR. DIAMOND: I am not sure anybody really knows into what category polycythemia vera falls. There are advocates of the idea that it is not a disease in itself but a beginning stage of myeloid leukemia. In fact, 20 or 25 per cent of patients with polycythemia vera ultimately have the features of chronic myeloid leukemia, and about 10 per cent of them have features of acute myeloid leukemia. I do not know whether this is truly a malignant tumor.

As for the second question, I might parenthetically add that the disease is malignant in the sense that it does kill patients. It kills a patient by virtue of its complications—thrombosis, usually, or hemorrhage.

As to the advisability of using radioactive phosphorus with or without preliminary venesection, our experience has shown that probably the best approach to the treatment of polycythemia vera with classic findings both hematologically and clinically, is to bleed the patient until the hematocrit reading and the hemoglobin level are normal, and then institute radioactive phosphorus therapy. If you do not bleed the patient, since it takes radioactive phosphorus about six weeks to begin to show any effect, clinically or hematologically, you will be starting treatment at a hematocrit of about 65 or even 70, and a hemoglobin level of 20 or 25 Gm. per 100 ml. instead of rather ideally at a hematocrit of 46 or 48 and a hemoglobin level of 15 or 16 Gm. By the time a rise occurs again, the phosphorus is beginning to work, and will bring the erythrocyte count, hemoglobin level, and hematocrit back to normal.

MODERATOR BURCHENAL: Dr. Karnofsky: "*Is there any advantage in using tourniquets on the extremities to protect the bone marrow in long bones during therapy with drugs that produce marrow depression?*"

DR. KARNOFSKY: We tried that eight or nine years ago, because in animals it is a feasible procedure. If one occludes the blood supply of the legs in a rabbit, injects a lethal dose of nitrogen mustard into the ear veins, and releases the tourniquet two or three minutes later, the marrow in the legs is spared and the rabbit dies with a normal white blood cell count.

On the other hand, there is little active marrow in the legs in human beings. We were not able to demonstrate that the toxic effect on bone marrow produced by the mustard was lessened by application of tourniquets to the legs. As it was a time-consuming procedure, we abandoned it.

MODERATOR BURCHENAL: Again, Dr. Karnofsky: "*Are any chemotherapeutic agents effective in the palliation of inoperable carcinoma of the esophagus?*"

DR. KARNOFSKY: No. No specific agent has been useful in carcinoma of the esophagus. If the tumor is localized, radiation therapy would be the most effective form of treatment. In epidermoid carcinoma, no drugs that we have tried had anything more than a transient effect on the growth of the tumor.

MODERATOR BURCHENAL: Dr. Diamond, or anyone else who would like to answer: "*What is the present status of treatment of multiple myeloma?*"

DR. DIAMOND: Chemotherapeutically, urethane is probably the agent employed most frequently. A dosage of from 3 to 4 Gm. daily is usually given in fractional amounts. The problem is severe gastro-intestinal as well as hematologic toxicity. Biochemically, there seems to be little reversal of the aberrations of the disease, whereas clinically the patient may improve, bone pain may be reduced, and constitutional symptoms may diminish.

Another chemotherapeutic group comprises the adrenocortical steroids and ACTH. They may effect dramatic improvement in a severely ill patient, but the remissions may be short-lived. These hormones are the only agents I know of that cause a return toward normal of the biochemical aberrations, such as hyper-

proteinemia and hyperglobulinemia. When a myelomic kidney is present, this condition also may be improved evanescently.

One must not forget radiation therapy. It has a definite place in the treatment of multiple myeloma, especially in areas of localized bone pain or pathologic fracture.

MODERATOR BURCHENAL: One more question: *"What is the role of atomic energy in the treatment of cancer?"*

It would seem to me that radioactive isotopes are in general more useful in the study of cancer for the purpose of labeling different compounds than in treatment of the disease. Cobalt, a source of high-energy radiation, can be used somewhat like a million-volt machine, or as a substitute for radium. I^{131} can be used in the treatment of thyroid carcinoma, providing the uptake of the tumor is adequate. P^{32}, as Dr. Diamond mentioned, is used in the treatment of chronic leukemias and polycythemia vera. Radioactive sodium does not localize particularly well, but it has been used in the treatment of chronic leukemias.

Dr. Karnofsky, or Dr. Diamond, are there any further uses of atomic energy?

DR. DIAMOND: There are a few others. This entire statement should be prefaced by saying that, at least to date, radioactive agents are much better in the diagnostic and biochemical aspects of investigation than in the therapeutic. Chromic phosphate may be used in the same way as radioactive gold, for instance (as Dr. Karnofsky mentioned) in the treatment of peritoneal and pleural effusions. Yttrium can be packaged, in a sense, like cobalt, and used in nylon applicators. Radon can be packed and used in gold-filtered seeds, needles, and the like, but the other artificial radioactive isotopes have not been particularly useful therapeutically.

MODERATOR BURCHENAL: Here is a question on Dr. Myers's presentation: *"In the osteoporosis associated with degenerative arthritis, the condition is thought to be progressing when the ratio of calcium to phosphorus is below 3.5 to 1. You have shown that when there is a response to therapy, the serum calcium level falls and the phosphate and alkaline phosphatase levels increase. Could this be due to the restriction of calcium intake for calcium excretion studies?"*

DR. MYERS: By this, I take it you mean, *"Could the decrease in the serum calcium level be due to the restriction of calcium intake?"* We do not think so. In patients whose intake of calcium was restricted, or even zero, and who were receiving intravenous fluids only, we did not observe any change in the level of serum calcium due to this restriction. There must be intermediation by some specific treatment.

SIMPLE SURGICAL THERAPY FOR OPERABLE CARCINOMA OF THE MAMMARY GLAND

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Carcinoma of the breast is important in the general cancer program because it is the most common site of malignant disease in women. It is estimated that 5 per cent of the women in this country are affected with the disease. Each year 62 new cases of cancer of the breast develop per 100,000 of the female population. In the United States the mortality from cancer of the breast per 100,000 female population has increased from 10 per cent in 1901 to 30.9 per cent in 1954; during that year 26,100 women succumbed to this disease (1).

From 1894 until about 1941 the thinking regarding the surgical treatment of carcinoma of the breast had been crystallized into the concept that when operation was indicated, radical mastectomy was the operation to be performed. During the years immediately following 1941 and continuing with increased vigor to the present time, there have been noteworthy departures from this concept. The departures have been in completely opposite directions; one group has advocated the more simple procedures while the other group has advocated extension of the operation outlined by Halsted in 1894.

Since even in the most skillful hands the conventional radical mastectomy may cause disfigurement, dysfunction and considerable psychic morbidity, it is extremely important to determine whether it is necessary to employ it routinely or to employ it at all. To date there is no proof that the results of radical mastectomy are better than those of simple mastectomy. Pathologists may theorize on the rationale of eradicating cancer by extended surgery, but in the final analysis it is the survival of patients that counts. In fact, if one reviews the accumulated reports from many groups throughout this country and abroad, it will be noted that the results with the simpler procedures are statistically better than those with radical mastectomies (2).

Halsted himself, not long after his published report on the treatment of carcinoma of the breast, was most unhappy about the results. Soon afterward he attempted to extend his original procedure. His more aggressive attitude indicates that: 1) the original procedure did not furnish the desired results, and 2) he hoped to obtain better results with extended procedure. He, very wisely, soon afterward remained content, but not convinced, that radical mastectomy would have to be his procedure of choice in the treatment of cancer of the breast "at that time." His original procedure must have fallen short of the mark, in his opinion, or he would never have attempted extension of his operation.

Today, many surgeons remain content, but are not convinced; they know that radical mastectomy is not the operation of choice for cancer of the breast. Many open-minded surgeons have resorted to other means; some have developed ideas

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for extension of the original procedure while others have followed the more conservative approach. The latter cannot be considered a regressive attitude. It is an honest attempt to improve results and survival rates and to offer an opportunity for treatment to a greater percentage of women with mammary cancer. This holds particularly true in patients considered to be in Stage III of the disease. In some clinics the tumors would be considered inoperable and referred for treatment by radiotherapy alone. In McWhirter's series (3) the five-year survival rate for locally advanced cases (comparable to Stage III) was 29 per cent for those treated by simple mastectomy and radiation. Bell (4) treated a group of 14 cases (Stage III) by simple mastectomy and radiation, and reported that 21.4 per cent of the patients were living and well five years later, as compared with 16.6 per cent among patients treated by radical operation alone. He expressed the opinion that radiation accounted for the better results in the first group and stated, "if a greater number of cases were represented, this might point more toward confirmation of McWhirter's ideas."

PATHWAYS OF DISSEMINATION

A comprehensive knowledge of the lymphatics is essential to the surgeon in the management of this disease. A brief review of the lymphatic spread and manner of dissemination of carcinoma of the breast is pertinent (Figs. 1 and 2).

The lymphatic drainage of the breast is so rich and replete with plexuses that the direction of spread of malignant cells through these channels is understandably unpredictable and fortuitous. Drainage is generally toward the skin surface where a subcutaneous plexus of lymphatic vessels permits the cells to be carried in almost any direction. The cells may migrate medially to the internal mammary nodes, laterally to the axillary nodes, or even to the inguinal nodes. These migrations may require months or years. Periods of quiescence are followed by fresh migrations. Cutaneous nodules are commonly observed in the vicinity of the lesion in advanced cases, or they may appear years after mastectomy. These so-called recurrences simply indicate macroscopic extension of disease that was present but not removed at the time of operation.

The lymphatic trunks that converge toward regional lymph nodes provide another method for spread of cancer of the breast. The spread occurs laterally toward the axilla, superiorly toward the supraclavicular nodes, medially toward the internal mammary group and mediastinal nodes, and inferiorly through the linea alba into the abdomen. The exhaustive studies of many qualified investigators have revealed that these paths of dissemination are never predictable. The lesion can spread to the supraclavicular nodes without involving the axilla; it may spread directly into the internal mammary group and mediastinum without involving the axilla; it can extend directly into the chest, over to the other breast and axilla, into the abdomen, and even down into the inguinal nodes.

One cannot consider the group of nodes about the axilla, neck, mediastinum and internal mammary region as completely unrelated and independent. Radiographic examination of calcified tuberculous nodes may clearly demonstrate their continuity in the supraclavicular and axillary regions. In cancer of the thyroid,

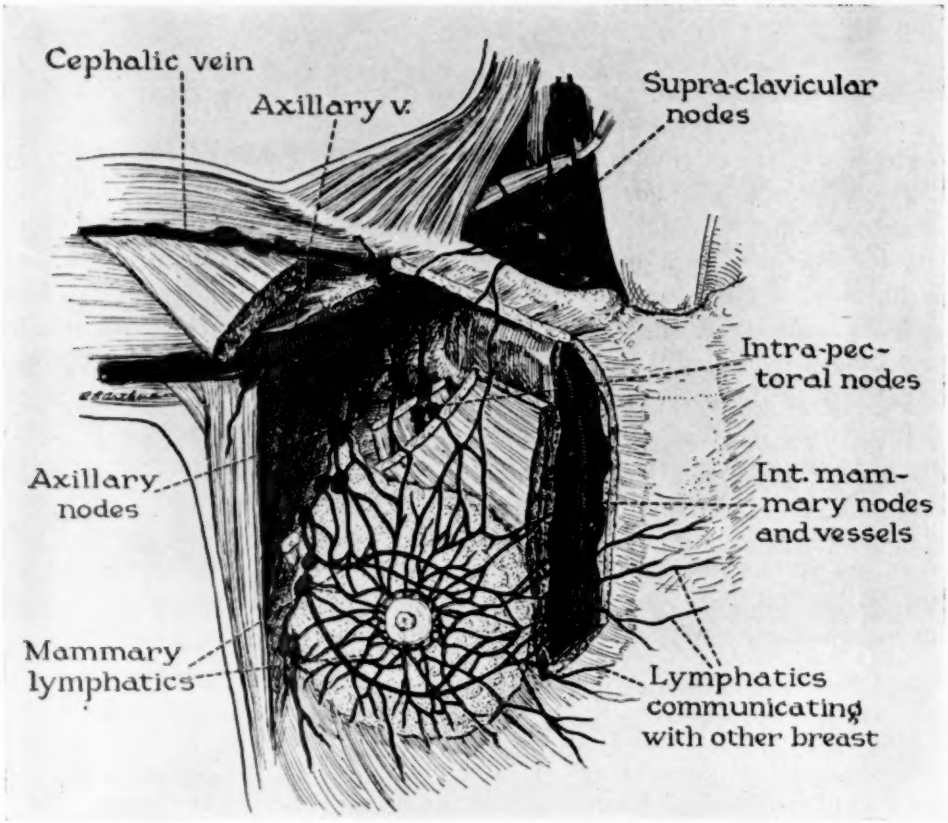

FIG. 1. The pathways of lymphatic drainage from the breast. (Modified from Rouviére, H.: Anatomy of the Human Lymphatic System. Ann Arbor, Michigan, Edwards Bros., Inc., 1938.)

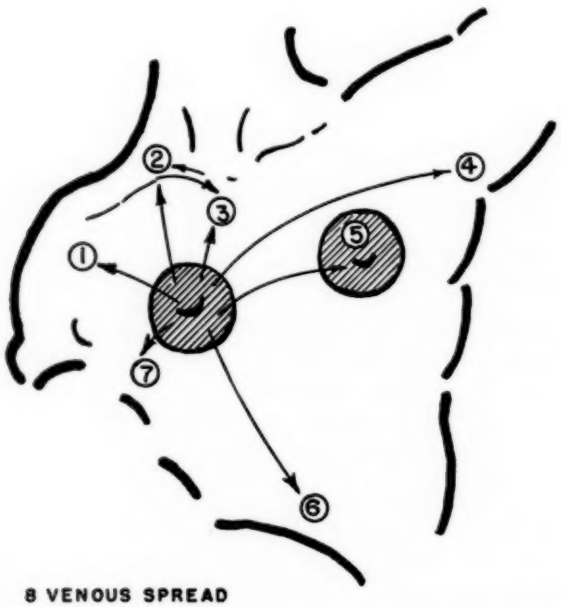

FIG. 2. Diagrammatic representation of the routes of lymphatic spread. 1. In 60 per cent of operable cases, the axillary nodes are involved. 2. In 33 per cent of these, the supraclavicular nodes are involved. 3. In 46 per cent of operable cases in which the axillary nodes are affected, the internal mammary nodes are also involved. 4. Spread to the opposite axilla. 5. Spread to the opposite breast. 6. Spread into the abdomen. 7. Spread directly into the chest. 8. Venous spread.

the presence of nodes in the lower portion of the neck is commonly associated with involvement of the axillary nodes. Here the disease spreads downward. If it can spread downward, it is fair to assume that it can also spread upward. It is, therefore, understandable that once cancer has spread to the axilla, it can readily extend throughout the entire chain and so involve the nodes which happen to be above the clavicle.

The continuity of the posterior cervical chain of nodes and the axillary group has been demonstrated in cases of cancer of the nasopharynx. This same posterior chain is not uncommonly involved in cancer of the breast.

The internal mammary chain of nodes, which is considered an important group by some and only a secondary group by others, bears a relationship to the supraclavicular nodes similar to that of the axillary group. Wangensteen and associates (5) found that 60 per cent of either the supraclavicular or internal mammary group were involved when the axillary group was affected.

It can, therefore, be appreciated that unless all these possible areas for dis semination of the disease are eradicated, any procedure may be doomed to failure. Wangensteen *et al.* attempted to do this, but soon realized its futility, and discontinued such an extensive procedure.

Proliferation along lymph channels is not the only method of dissemination. What is even more treacherous, is the spread of the disease by venous channels. This is much more common than we have realized. In 59 per cent of a series of 107 patients with operable cancers of the breast, lung, stomach and colon, Engel of Stockholm (6) found cancer cells free in the blood of the veins that drained the cancer areas. Among these, 35 per cent of Grade II cancer patients, 78 per cent of Grade III, and 100 per cent of Grade IV patients had cancer cells in the blood. It has been stated that in perhaps 10 to 20 per cent of cases of cancer of the breast there is dissemination through the blood stream. This method of dissemination can well explain the all too frequent case of a patient with a small lesion, no regional adenopathy, and distant metastases.

The location of the lesion in the breast with regard to prediction of the involvement of a particular group of nodes is another point for emphasis. Handley and Thackery (7) showed that the internal mammary group of nodes is involved in a high percentage of cases of cancer of the breast. Other investigators have pointed out that the internal mammary group of nodes is more likely to be involved when the breast lesion is in the medial quadrant, and they have devised ultraradical procedures to remove all involved tissue (8). On the other hand, Hutchinson (9) found no correlation between the location of the lesion in the breast and the incidence of mammary node involvement in his study of 81 consecutive cases.

SURGICAL CONSIDERATIONS

Adequate surgery for cancer is not based on detecting affected lymph nodes. The area of lymphatic permeation in fascial planes is a basic consideration. There should be an attempt to maintain the integrity of the cancer field. This has been the purpose in the extension of operations for the treatment and cure of this dis-

ease. Even with the most honest and aggressive type of surgery, this cannot possibly be accomplished in treating cancer of the breast if one bears in mind the anatomy of the lymphatics and the pattern of lymphatic spread. Radical mastectomy is as discontinuous a procedure as simple mastectomy; in fact, it is more harmful, for it opens up more channels for dissemination. It is only with adequate radiation therapy, at this time, that we can hope to extend suitable treatment to areas that are inaccessible by any type of surgery.

The principle upon which radical mastectomy was originally based was that cancer of the breast generally would spread in an orderly fashion and in one direction, *i.e.*, into the axillary nodes. It is obvious from the brief description of the lymphatic spread of this disease that this is not true in most cases; by the time the patient presents herself for therapy, many of the other nodes are involved. Even the ultraradical surgical procedures do not encompass all these avenues of spread. Removal of the breast, axillary nodes, supraclavicular nodes, internal mammary nodes and even part of the chest wall does not guarantee a cure. Halsted appreciated this soon after he became interested in this field of surgery.

Heroic attempts have been made by many honest surgeons both here and abroad to extend the scope and magnitude of radical mastectomy. The reports of Wangensteen (5) and of Dahl-Iversen (10) and associates have not been encouraging. It will be interesting to note the five-year survival rate reports of others when they are made available.

The ultraradical procedures (5) have been most valuable in adding knowledge about the lymphatic spread of cancer of the breast. The results obtained have simply fortified the belief that both radical mastectomy and the ultraradical technics cannot be considered procedures of choice because of the unpredictability of the lymphatic spread from any quadrant of the breast.

Haagensen triple biopsy has been a noteworthy contribution. It not only has provided additional valuable data about the dissemination of the disease, but is also an indication of a trend toward the performance of less radical mastectomies on patients who ordinarily would be considered suitable candidates for the classic Halsted procedure.

The five-year survival rates of patients treated by the simple methods, with or without radiation, have become increasingly encouraging. Williams, Murley and Curwen (11) concluded that, with or without radiation, simple mastectomy yielded better results than radical mastectomy at St. Bartholomew's Hospital. Meyer and Smith (12), in their report on an unselected group of cases, noted an 8 per cent higher survival rate among patients treated with the simpler procedures than among patients who had undergone radical mastectomies. Small and Dutton (13), Byrd and Conerly (14), Orr (15), Garland (16), and Deaton and Bradshaw (17) have all come to similar conclusions. Moreover, Deaton (2), in a survey of the world literature, reported that the survival rate following simple mastectomy was 5 per cent higher than that following radical mastectomy.

The present controversy concerning the surgical management of cancer of the breast was precipitated by McWhirter (3) of Edinburgh, who subjected a popu-

lation group of more than 1 million people to a careful clinical study. All cases of cancer of the breast that occurred in this population group were included, regardless of how they were treated, or whether they remained untreated. His survival rates for patients undergoing simple mastectomy and radiation were 10 per cent better than for patients undergoing radical mastectomy. His supplementary report, including data on ten-year survival rates, is even more encouraging.

The poor results attributed to radiotherapy at the time of his study (1941 to 1947) is understandable. It was during the war years when the equipment and personnel were not satisfactory. These unfortunate complications are avoidable today with the better knowledge of radiation therapy and using the protracted method of treatment suggested by McWhirter and others. The recurrence rate in McWhirter's radiotherapy series is not unusually high when one considers that some clinics report a rate as high as 82 per cent and others a rate as low as 2.5 per cent. Furthermore, the recurrences appeared mostly outside his field of treatment; this would now be avoidable with the more adequate standards for radiotherapy.

Most physicians today agree that adequate cancerocidal doses of radiation are prohibitive to the host. At present, the best that can be expected is incarceration of potentially malignant cells that are rendered at least temporarily inactive, in the hope that so-called host resistance may be altered to the point where cells can be maintained in an impotent state for an extended period of time.

The five-year survival rate is not a reliable criterion, for we are all familiar with the fact that there may be a recrudescence of the neoplastic processes almost any time after a five-year clinical arrest (13). This is due to uncontrollable factors such as host resistance, or reactivation of the virulence of the offending cells, for which we have no defense either surgically, radiologically or, as yet, chemically. These factors, about which we know so little, have caused surgeons with open minds to reconsider their form of surgical therapy.

It may be unfortunate that all patients treated in a hospital are not obliged to return there for follow-up study. A particular hospital may not be able to record the complete and true results of postoperative radical mastectomies, because many patients refuse to return to that institution. For many years, at one of the municipal hospitals, I saw the end-results of many cases of radical mastectomy performed elsewhere. The complications ranged from frozen shoulders and injury to the brachial plexus to lymphangiosarcoma following lymphedema of the arm.

I have no quarrel with the surgeon who, because of his training, remains loyal to the traditional modalities of therapy, even though they be outmoded. However I feel strongly that such beliefs should not be imposed upon the profession at large.

To state that one method will provide the best results is fallacious reasoning. "Individualization of therapy" can be applied just as well in the treatment of cancer of the breast as in the treatment of other diseases.

COMMENT

Surgery is the best modality of therapy for operable cancer of the breast, and simple mastectomy with postoperative radiation is to be preferred to radical mastectomy. The removal of accessible axillary nodes can be accomplished without additional morbidity (18) for purposes of prognosis rather than for complete eradication of the disease (19).

My enumeration of objections to radical mastectomy may lack convincing completion, but the catalogue of errors is a lengthy one; to mention all and moralize on each would be tedious and wearisome. I hope to arouse and fertilize the imagination of those who maintain an open mind.

Perhaps we have reached the peak of advances in the surgical treatment of breast cancer, and further progress will be dependent upon the discovery of etiologic factors or the use of chemotherapeutic agents.

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PROCHLORPERAZINE IN THE MANAGEMENT OF RESTIVE AGED PATIENTS

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In a recent study (1) of prochlorperazine as an adjunct in the treatment of tuberculosis, we found the drug to be a tranquilizer of distinct value in helping patients to adjust to hospital confinement and discipline, as well as an antiemetic of considerable merit. Among those given prochlorperazine were several elderly patients whose behavior and emotional condition were markedly improved by the drug.

These observations led us to evaluate prochlorperazine specifically in a group of geriatric patients, in the hope of alleviating the anxiety, tension, fear, agitation, hostility and other symptoms of emotional disturbances commonly found in aged, physically ill persons.

MATERIALS AND METHODS

Fifty aged patients were treated with prochlorperazine.[1] They ranged in age from 60 to 88 years; almost half were older than 75. Nineteen were men and 31 were women. Twenty-one were treated in private practice; 29 were hospitalized in public or private hospitals or sanatoriums.[2]

At the time of the study, all patients were being treated for one or more organic disorders, including cancer, renal calculus, osteoarthritis, atherosclerosis, diabetes, biliary dyskinesia, and parkinsonism. In addition, 26 patients suffered from persistent nausea and vomiting and 11 had severe persistent pain. All of the 50 exhibited prominent psychic distress which persisted despite treatment with tranquilizers, hypnotics, and therapies specifically directed toward the organic symptoms. During the evaluation of prochlorperazine no other tranquilizing agent was administered, although treatments for the organic disorders were continued.

The daily dose of prochlorperazine was individualized. Medication was begun as one 10-mg. sustained-release capsule morning and evening. (In sustained-release capsule form, the dose of prochlorperazine is divided into many small, coated pellets which dissolve at different rates and release the drug slowly over a period of ten to twelve hours.) Depending upon the patient's reaction, the dose was increased (or decreased) until the optimum response was obtained, or side-effects interfered.

Because the patients suffered from a variety of organic disorders, most of which were chronic and many of which were terminal, it was difficult to rate the responses except in a general way. The following ratings were used: a) *Good*—the patient had adjusted emotionally to his disease, was no longer anxious, fearful, tense or agitated; nausea and vomiting were controlled; or pain was reduced in severity or was no longer a problem. b) *Fair*—the patient had become more relaxed and quiet in contrast to pretreatment behavior; nausea and vomiting were less troublesome, although not completely relieved; or pain was somewhat more bearable. c) *Poor*—the patient showed little or no improvement over the pre-

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[1] Compazine; Smith, Kline & French Laboratories, Philadelphia.

[2] The following Philadelphia hospitals and sanatoriums participated in this evaluation: Rush Hospital (Geriatric Unit), Wolffe Hospital, Anglecott Sanatorium, and Fairview Nursing Home.

treatment condition and remained anxious, fearful, tense or agitated; nausea and vomiting were unabated; or pain remained severe and intractable.

RESULTS

All patients received sustained-release capsules of prochlorperazine twice each day, morning and evening. Optimum daily doses were found to be: 40 mg. (1 patient), 30 mg. (26 patients), 20 mg. (21 patients), and 10 mg. (2 patients).

Before therapy with prochlorperazine, 44 patients showed extreme anxiety, fear, tension or agitation. Thirty-nine of them had received tranquilizers but had failed to improve. With prochlorperazine, 37 patients (84.1 per cent of the group) had a good response, 4 (9.1 per cent) had a fair response, and 3 (6.8 per cent) had a poor response. Patients who responded did so within two weeks after the beginning of therapy.

During treatment with prochlorperazine, patients were notably less apprehensive and considerably more cooperative than they had been. Although they slept better at night and obtained more rest during the day, they were not sedated, as indicated by their cheerfulness and alertness during the day. Many institutionalized patients began to participate in ward activities, complained less of their pains and troubles and talked more about things of general interest. Visiting hours seemed less tearful and emotionally charged than previously. Morale among patients, their families, and the nursing personnel improved as wards became quieter and more pleasant.

Similar improvement was observed in patients living at home. They became less of a burden to their friends and families as they improved in behavior and outlook. Some patients who had been inactive for years began to perform simple household tasks. Most of them became neater and more careful about their appearance and personal habits. As a result of these improvements, there was noticeably less friction between the patients and their families, friends and neighbors.

Eleven patients suffering from renal calculi, carcinoma or other disorders had severe pain which was not controlled satisfactorily by sedatives or narcotics given alone or with tranquilizing drugs. When prochlorperazine was administered along with sedatives or narcotics, the results were good in 7 patients, fair in 3, and poor in 1. Although prochlorperazine did little to affect the intensity of pain, the response of the patients to pain was modified. Most of them remained aware that the pain persisted, but they were no longer upset by it and could turn their attention to reading or conversation and thus ignore the pain.

Before therapy with prochlorperazine, 26 patients suffered from severe persistent nausea and vomiting due to such disorders as biliary dyskinesia, gastritis or cancer. Twenty-three of these had failed to respond satisfactorily to therapy with anti-emetics, antispasmodics and tranquilizers. With prochlorperazine, 20 of the 26 patients (77.0 per cent of the group) had a good response, 4 (15.4 per cent) had a fair response, and 2 patients (7.6 per cent) had a poor response. Control of nausea and vomiting was often attained within the first hour of therapy.

Mild, transient untoward effects were noted in 10 cases. Nine bedridden patients became drowsy with a daily dose of 30 mg. of prochlorperazine (one 15-mg. sustained-release capsule morning and evening). Drowsiness disappeared when the dosage was reduced to one 10-mg. sustained-release capsule morning and evening. Another patient was slightly agitated for the first two days of therapy with 20 mg. daily. The excitation disappeared spontaneously with no change in dosage. No other untoward effects were observed.

SUMMARY AND CONCLUSIONS

Fifty geriatric patients, all with organic illness accompanied by emotional disturbances, were given prochlorperazine in sustained-release form for three to nine months. In some cases, the drug was used as an anti-emetic as well as a tranquilizer.

Of 44 patients who showed extreme anxiety, fear, tension or agitation, 37 (84.1 per cent) had a good response to prochlorperazine, 4 (9.1 per cent) had a fair response, and 3 (6.8 per cent) had a poor response. Of 11 patients who suffered from severe intractable pain, 7 had a good response, 3 had a fair response, and 1 had a poor response. Of 26 patients who suffered from nausea and vomiting, 20 (77.0 per cent) had a good response, 4 (15.4 per cent) had a fair response, and 2 (7.6 per cent) had a poor response.

Mild, transient untoward effects were noted in 10 patients. Nine experienced drowsiness, which disappeared promptly when dosage was reduced. One patient was slightly agitated during the first two days of therapy; the agitation disappeared spontaneously with no reduction in dosage. There were no other side-effects.

Prochlorperazine proved to be an effective drug for relieving mental and emotional distress. Aged patients who had not responded satisfactorily to other therapy received prompt relief of anxiety, tension, fear and agitation. The mental and emotional disturbances which often accompany old age were reduced during prochlorperazine therapy and the patients became more cheerful, cooperative, and better able to help themselves. Prochlorperazine also proved to be an effective drug for controlling nausea and vomiting and for helping to relieve severe, intractable pain.

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A NEW STIMULANT SUPPLEMENT FOR THE GERIATRIC PATIENT

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Although the degenerative changes of advancing age cannot be halted, numerous clinical studies on aging and the aging process reveal that good nutritional and steroidal support combined with mild stimulation go far to provide a more healthful, vital old age. The need for such support in the older age groups can be attested to by the marked upsurge in compounds specifically designed for this purpose. One of these preparations was brought to our attention recently.

The compound (Ritonic)[1] contains Ritalin, a non-amphetamine stimulant which induces alertness, improves psychomotor performance, and does not give rise to the usual side-effects of similar compounds. It rarely causes hyperexcitability, an exaggerated sense of well-being, elevation of blood pressure, tachycardia, depressive rebound or inhibition of appetite. Since the diet of elderly people usually lacks many of the essential dietary elements, and since steroids are valuable for treatment of many common disorders of the elderly because of their anabolic action, these factors were added. Specifically Ritonic contains: Ritalin (5 mg.), Metandren (1.25 mg.), Eticylol (5 μg.), vitamin B_1 (5 mg.), vitamin B_2 (1 mg.), vitamin B_6 (2 mg.), vitamin B_{12} (2 μg.), niacinamide (25 mg.), and dicalcium phosphate (250 mg.).

Clinical evidence indicates that this compound is of particular value in elderly patients who complain of lassitude, loss of appetite and lack of interest. Natenshon (1) studied Ritonic in 92 geriatric patients with a wide variety of such complaints and obtained excellent results in 78 per cent. According to this clinician, Ritonic is "a safe, effective geriatric supplement, that can be used in practically all types of geriatric conditions without harmful effect." Other investigators have noted that their patients were "more alert," "more active," "more sociable," and had "improved appetite."

Our study with this compound ran almost a full year, from April 27, 1957 through April 7, 1958. There were 46 females and 7 males in the series, ranging in age from 42 to 82 years. All of these patients had various combinations of postmenopausal symptoms, mild anxiety, osteoporosis, obesity, mixed types of arthritis, osteoarthritis and rheumatoid arthritis. They were treated in the office. The dosage of Ritonic varied from 1 capsule daily to 1 capsule mid-morning and mid-afternoon.

Improvement was noted in 43 of our 53 patients. There was no change in 8, and the medication was discontinued in 2.

In general, there were no untoward results; blood counts, blood pressure and urinalysis findings were not affected. There were few side-reactions. One patient discontinued the capsules after several days because of dizziness; however, she was unable to tolerate any medication by mouth. One patient complained of

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[1] Trademark, CIBA Pharmaceutical Products Inc.

nausea. A rash which developed on the hands and face of another woman necessitated discontinuance of medication. Weight gain due to sodium retention was noted in 1 subject, but this was probably unrelated to the drug. There was no evidence that Ritonic increased anxiety or tension.

SUMMARY AND CONCLUSIONS

In a group of 53 patients who were treated with the stimulant-supplement, Ritonic, 43 reported an increase in alertness, vitality and sense of well-being. They also felt less fatigued and were anxious to participate in household activities, whereas previously they had been unwilling or unable to cooperate.

Ritonic is a useful vitamin-hormone-stimulant preparation for patients past age 40 who come to the physician's office complaining of the vague symptoms usually related to natural degenerative changes found at this time of life.

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REHABILITATION OF CHRONICALLY ILL GERIATRIC PATIENTS: ADJUNCTIVE USE OF AN ATARACTIC AND NUTRITIONAL-HORMONE PREPARATION

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The management of geriatric and chronically ill patients has always been a challenge to medicine and to society. Progress in their care requires continued research in the field of gerontology, and a comprehensive therapeutic approach. The latter must include amelioration of symptoms, correction or retardation of pathologic or progressive processes, and reasonable restoration of physiologic and mental functions. This entails consideration of pathologic conditions reflecting the biologic involutional process, stress and strain, dietary factors, the emotional status of the individual, and his socio-economic problems.

A therapeutic program for the patient should include a plan specifically directed at the pathologic and functional disturbances, in addition to a supplementary and complementary program. Owing to more enlightened medical concepts, the concomitants of so-called normal aging are now reversible to a clinically significant degree (1). For example, the beneficial effects of endocrine therapy (2) and vitamin and mineral supplementation (3) in the aged have been substantiated. Agitation, anxiety, and emotional unrest are frequently associated with chronic illness and the involutional process. Such apparently neurotic symptoms may occasionally assume serious proportion in the form of hostility (4). There is no substitute for a psychotherapeutic approach, using compassion, understanding, and reassurance; but tranquilizers (5) and endocrine preparations (6) can be of additional benefit to the emotionally disturbed patient.

It is the purpose of this paper to 1) reiterate the importance of a comprehensive therapeutic approach, 2) substantiate and confirm the clinically beneficial effect of such a complementary program adjunctive to specific therapy in rehabilitation, and 3) encourage other physicians to use all the pharmacologic agents available for the treatment of the geriatric patient as a whole.

METHOD

Clinical observations were made on 50 patients (27 males and 23 females) selected on the basis of the "geriatric syndrome" of Dufficy (7), characterized by minor complaints of malaise, lassitude, fatiguability, dyspepsia and anxiety-tension states. These patients were from 46 to 81 years of age and were seen in the author's practice and at the Forest Hills Nursing Home and Rehabilitation Center. Most of them were chronically ill and required specific therapy with digitalis, nitroglycerin, hypotensive drugs, antidiabetic agents and muscle relaxants. All patients had had their major complaints and had undergone specific treatment for more than three months.

A complete history was taken on each patient, and a complete physical examination was made, which included a prostatic examination in the males, urinalysis, and a hemoglobin determination prior to initial therapy. The urinalyses and hemoglobin determina-

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tions were repeated at intervals varying from one to three months. The pathologic entities were usually multiple and included climacteric symptoms, muscular aches, arteriosclerosis, arthritis, diabetes, post-fracture states, hemiplegia, hypertension, cardiovascular disease, and parkinsonism.

The patients were treated with a nutritional-hormone compound (Neobon)[1] and hydroxyzine (Atarax)[2] in addition to the specific therapy. These 2 medications in liquid form were mixed in a ratio of 1 to 2 teaspoonfuls of Atarax (2 mg. of hydroxyzine per cc.) to 1 teaspoonful of Neobon. The mixture was given twice or three times daily, and the dosage was adjusted according to the response of the patient. The duration of treatment ranged from one week to one year.

The liquid form of medication was preferred, as it offered ease of administration and greater flexibility of dosage and combination; moreover, the nutritional-hormone supplement in this form permitted inclusion of small amounts of alcohol. Hydroxyzine was selected because it appears to induce a more desirable state of calmness and peace of mind in this type of emotionally disturbed patients than any drug used previously (8). It is also effective in cardiac arrhythmias (9), and thus can be used prophylactically or therapeutically in geriatric patients with arteriosclerotic heart disease.

Parkinsonism, either overt or latent, is frequently associated with arteriosclerosis in the central nervous system. Some diphenylmethane derivatives (10) such as benactyzine are known to be beneficial (11). Since hydroxyzine has never precipitated extrapyramidal symptoms, and since its structure is that of diphenylmethane-piperazine, it likewise may benefit patients with parkinsonism.

The combination of oral estrogen and androgen in low dosage is synergistically effective in producing anabolism and a sense of well-being; thus a predominating effect by any single component is overcome (12, 13). The nutritional-hormone preparation used in this study contains amphetamine to prevent over-eating and obesity (14), vitamins and minerals for the correction of deficiencies often found in the aged (15), and thyroid for lipotropic action (16). Subtle hypothyroidism is frequently overlooked in geriatric patients and thyroid therapy often elicits a striking response (17).

CLINICAL RESULTS

During treatment of these 50 patients with cardiovascular, antidiabetic and other specific agents, physical sluggishness, functional and emotional disturbances, and the "geriatric syndrome" required attention. This suggested the use of an ataraxic combined with a nutritional-hormone supplement. The addition of these preparations to our rehabilitation procedures had a dramatic impact on the well-being of these patients.

Significant improvement was noted in 41 (82 per cent) of the 50 patients, minor subjective improvement in 5 (10 per cent), and no change in 4 (8 per cent). The criteria for this evaluation were both subjective and objective. Patients were considered to be in the "significant improvement" category if, 1) they stated that they felt better in general, 2) if members of their family noted improvement, and 3) if there was objective evidence of improvement. A marked reduction occurred in complaints of diffuse aches and pains, dizziness, and digestive disturbances. No adverse upper gastro-intestinal symptoms were observed. Appetite increased and sleep patterns became steadier. Improvement was also

[1] Neobon (J. B. Roerig & Company) in liquid form contains gonadal hormones, essential hemopoietic factors, digestant enzymes, and various mineral, nutritional and protein factors, in dilute alcoholic solution.

[2] J. B. Roerig & Company (Division Chas. Pfizer & Co., Inc.).

noted in the general physical appearance and condition of these patients. Many who had depended greatly on other persons prior to therapy made greater efforts in helping themselves and were more cooperative. The condition of debilitated patients improved, and some of the obese patients lost weight. Hypertension was reduced in most cases, the fall in blood pressure ranging from 20 to 30 mm. Hg. Hemoglobin levels increased. These responses to our comprehensive care program occurred within one to three weeks after initiation of this supplemental therapy.

In neurologic patients there was a variable reduction in spasticity, both objectively and subjectively. Tonicity was lessened and some patients exhibited greater ease in voluntary motion. Convulsive seizures occurred less frequently and emotional lability and crying spells diminished. The rigidity and tremors were less tiring to the patients; this permitted greater function. No adverse effects on the blood, liver, or kidney were noted after one year of therapy.

The slight improvement reported by 5 patients was not corroborated objectively by members of the family, nor by our physical therapists.

Increased fatigue, lethargy, slight headaches and loose bowel movements occurred in some patients who were taking the medication three times daily, but usually subsided when the dosage was reduced. These side-effects were noted within two to four days after commencement of therapy and could not be considered as coincidental. Although one of the patients discontinued therapy because of loose bowel movements, the others considered this result as a welcome relief from their usual hypotonic constipation. The following are 3 short illustrative case histories:

Case 1

H. D. was a 56-year-old man with diabetes, hypertension and left hemiplegia. Increase in severity of the left-sided involvement had been gradual and progressive, but function had returned to all but his left upper extremity. The rehabilitation program was hampered by frequent attacks of angina, dypsnea on mild exertion, emotional lability and irritability. Medications prior to referral were antidiabetic drugs, muscle relaxants, digitalis and nitroglycerin. When the Atarax-Neobon preparation was administered, the patient showed marked improvement in his tolerance to exercise therapy, required less nitroglycerin, and his emotional lability decreased. There was a decrease in the severity of spasticity in his left upper extremity, and enhanced voluntary control. Re-employment in his old occupation as a short-order cook was not possible, but the patient was encouraged to develop an avocational interest.

Case 2

Mrs. G. D. was a 71-year-old woman with arteriosclerosis and Parkinson's disease. She was confined to bed most of the time, and manifested hostility, anxiety, coarse tremors, arthritis with osteoporosis of the spine and moderate anemia (65 per cent hemoglobin). A rehabilitation program was set up at home. Nutritional-hormone therapy with adjunctive use of hydroxyzine and hematinics was prescribed. The patient began to improve, became ambulatory, and at present cares for herself. She is much more cheerful and is considering a trip to California to visit a son.

Case 3

Mrs. E. M., a 74-year-old woman, was referred because of intractable severe burning pain in her right thumb and index finger, burning pain in her mouth and in the soles of her feet, diffuse muscular aches and pains, and right hemiparesis sustained six months previously. The pain in her right hand interfered with some of her activities. Blood pressure was 200/150. Examination revealed diffuse arteriosclerosis, diabetes, peripheral neuropathy and anemia. Nutritional-hormone supplements, ataractic therapy and hematinics were prescribed, and physical therapy was instituted. In the course of treatment, right facial palsy developed. Her daughters have reported that there has been a lessening in emotional turbulence, a marked diminution in hypochondriacal complaints, and fewer remarks about the burning in her hand. At present the patient is able to use the right hand in her housework. Her blood pressure had declined to 170/95.

The cases cited could be supplemented by many others. Patients exhibiting the menopausal syndrome and the "geriatric syndrome" without presentation of a distinct disability, purposely have not been discussed, but the therapeutic results were no less dramatic in these instances. It must be re-emphasized, however, that Neobon and Atarax, in their supplemental and therapeutic function, constituted only one part in the total program and comprehensive care of these patients.

COMMENTS

A comprehensive program of rehabilitation should preserve and restore functions as well as effect a wholesome outlook and more active life. Preventive or prophylactic care of our aged, though strongly recommended, is still only rarely accepted by them. They seek medical care primarily for acute illness, because of aggravation of chronic complaints, or to achieve restoration of lost functions. It behooves all practitioners to utilize these opportunities for the initiation of prophylactic and comprehensive care.

There are no magic medications and no panaceas for rejuvenating our aged. It is, however, possible to ameliorate and retard the progression of biologic involutional processes. The influence of the endocrine system on these processes and the beneficial effects of hormone preparations are well documented (13, 18, 19). Such factors as nitrogen metabolism, bone metabolism, blood formation, cardiovascular function and wound healing merit greater consideration of endocrine therapy. The alleged danger of carcinogenesis in hormone therapy has not been substantiated (20).

Vitamin and mineral deficiencies frequently observed in the aged population (15, 21) may be partially dietary and partly malabsorptive. Nutritional-hormone supplementation is indicated in these instances. Psychosomatic tensions may become manifest as increased muscular tonus, increased spasticity in cases with pyramidal-tract involvement and greater rigidity and tremor in Parkinson's disease. Patients with "little strokes" respond well to hydroxyzine therapy (22), and tensions and agitation are markedly diminished in the aged (23).

SUMMARY

The purpose of this study was the evaluation of a nutritional-hormone supplement (Neobon) and a tranquilizer (Atarax), both in liquid form, as adjunctive agents in a comprehensive approach to the total care of chronically ill geriatric patients.

Previous reports of the favorable effects of each preparation were substantiated by the general beneficial action of the combined therapy in a group of 50 patients. The liquid form of the medications permitted greater flexibility in dosage ratios and amounts, and greater ease both in administration and in combination with other specific drugs.

Results were encouraging. Of the 50 patients treated, 41 (82 per cent) were significantly benefited; in 5 (10 per cent) there was minor subjective improvement; and in 4 (8 per cent) there was no change. Adjustment of dosage was necessary in some patients who experienced side-effects such as lethargy, increased fatigue, loose bowel movements and slight headaches.

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ENZYMATIC FACTORS IN PROTEIN MALNUTRITION OF THE GERIATRIC PATIENT

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In the past two decades, medical advances on a wide variety of fronts have markedly increased the life span. That segment of our population in the "over 65" age group has expanded to almost 10 per cent of the total census, and now numbers about 15 million. It follows logically that there has been a renewal of interest in the normal and pathologic physiology of geriatric nutrition, along with concerted investigations and extensive research into the field of the chronic and degenerative diseases which occur with increased prevalence in the later years of life.

Imbalance in the digestive mechanism probably produces the most frequent clinical symptomatology observed in general office practice today (1). Commonest among complaints of the aged are matters either vaguely or definitively referable to the gastro-intestinal tract. The harried and overburdened clinician is often prone to brush aside as "dyspepsia," indigestion or psychosomatic manifestations, such frequent complaints among older patients as "gas," flatulence, abdominal discomfort, nausea, anorexia, heartburn, sourness, frequent foul stools, constipation and similar disorders. Medical prejudice and uncertainty about nutritional disturbances in large measure accounts for the difficulties in evaluating the more obscure gastro-intestinal conditions (2).

Routine questioning and follow-up laboratory and radiologic examination often reveal nothing of particular significance, and the complaints are usually treated symptomatically. Frequently the patient is temporarily relieved, only to return with the same story a few weeks later; more often than not, there is no apparent change in the clinical picture, and after the gamut of a long series of remedies has been run, either the elderly patient changes doctors, or vice versa. Such therapeutic failures are ripe targets for purveyors of nostrums and quack remedies, and the patient may fall into the hands of faddists or charlatans who take full advantage of this medical failure.

One aspect of protein malnutrition in the aged which has not received adequate attention or investigation commensurate with its intrinsic role in producing poorly defined gastro-intestinal symptoms is the problem of pancreatic dysfunction and insufficiency. In the experience of the average clinician, the lack of definitive laboratory tests to reveal subacute, chronic or latent insufficiency of the exocrine pancreatic function is probably the prime reason for difficulty in making the diagnosis. In addition, the vagueness and nonspecificity of the clinical picture make clear-cut identification of mild to moderate inadequacy of the pancreas a difficult procedure.

Unless there is fulminating acute pancreatitis or a primary neoplasm in the

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gland, the occurrence of pancreatic dysfunction is only infrequently recognized during life (3, 4). In 400 consecutive necropsies in persons over 20 years of age, Pollak (3) found 80 instances of either gross or microscopic disease of the pancreatic acini or enzyme-secreting cells. In only a small percentage of these 80 was pancreatic disease (other than diabetes mellitus) recognized during their lifetime. In 19 of the 22 diabetic subjects, the pancreas showed hyalinization and other changes involving the acinar cells.

THE ROLE OF THE PANCREAS IN PROTEIN METABOLISM

The role of the exocrine pancreatic secretions in hydrolyzing ingested proteins into the constituent amino acids preparatory to absorption is well known and needs no special emphasis here. When inadequate pancreatic enzymes bring about only a partial or incomplete breakdown of ingested protein, the intermediate products are acted upon by intestinal flora with the release of numerous amines rather than amino acids. These are readily absorbed into the portal circulation, and those amines which are toxic may produce numerous untoward and serious reactions in the host. Among these are a hypotensive effect and a histamine-like shock effect (5, 6). Many other such untoward reactions, on the surface seemingly quite unrelated to the pancreas, occur frequently. Further evidence of the pancreas' protective function over the liver is suggested by the recent studies on choline, "lipocaic," and other yet to be isolated lipotropic factors resulting from pancreatic proteolytic activity. These are reputed to play a vital role in preventing degenerative changes and fatty infiltration of the liver.

A multitude of causes predisposes the aged patient to protein malnutrition. Inadequacies of dietary protein or its metabolism are the commonest and most obvious factors in geriatric practice. The aged person's desire for simple mushy carbohydrates (occasioned by either social or economic necessity), frequent achylorhydria, or even lack of proper dentures may provide the basis for deficient protein intake. Many older patients avoid a high or even an adequate protein diet because instinctively they feel that their gastro-intestinal symptoms are aggravated by this essential food item.

The concept that older persons have lower concentrations of digestive enzymes enjoys wide acceptance (7, 8). Deterioration of visceral parenchyma as a sequence to generalized arteriosclerosis generally attends the sixth, seventh and eighth decades of life. Connective-tissue replacement of secretory cells is the visual counterpart of tissue aging as seen at necropsy. Pollak found a high degree of correlation of exocrine tissue alterations with the changes in the endocrine portions of the pancreas in his series of autopsies when diabetics were involved. Lowenstein (9, 10) carried this concept into the level of actual clinical therapy in his handling of the diabetic patient.

In clinical practice, one less apparent circumstance which also receives scant attention in considering protein malnutrition is the frequency of albuminuria. Most commonly, loss of protein in this form, or failure of hepatic synthesis associated with chronic congestive heart failure, chronic nephrosclerosis, or other cardiorenal disorders eventually manifests itself in a diminution of the con-

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centration of total serum proteins. Alterations in the renal tubular or glomerular anatomy, whether through cardiovascular disease or chronic inflammatory changes, permit the loss of body protein in the form of albumin in the renal filtrate. The albumin-globulin ratio thereby diminishes in value or eventually becomes reversed. The electrophoretic studies of Chesrow *et al.* (11) indicate clearly the lowering of the serum albumin level in a general geriatric population.

It is an accepted fact that in order to maintain proper repair and replacement of all essential body tissues, and to provide the amino acids necessary for the synthesis of indispensable hormones, enzymes, tissue proteins, vitamins and intrinsic factors, both adequate protein intake and utilization are required. It is conceivable that many of the "degenerative" diseases of old age are basically reflections of nutritional deficiencies, due to interference with the proper protein utilization (12, 13) and/or insufficient intake in the diet. Further loss of serum protein in the form of albuminuria extends this depletion. These factors, alone or in combination, deprive the older patient of the basic building material (amino acids) (14) so vitally needed for cellular anabolism, tissue repair and production of essential body secretions.

CLINICAL STUDY

Methods

A study was undertaken with 32 geriatric patients for a period of eight to ten months, to determine whether by supplying proteolytic enzyme supplements and a high-protein diet, we could bring about a reversal of the process of diminishing serum protein concentration in the aged.

The patients ranged in age from 62 to 89 years, and were empirically grouped as follows:

1. Eighteen patients with chronic congestive heart failure, due to either long-standing hypertensive cardiovascular disease, rheumatic valvular disease, post-coronary syndrome, or nephrosclerosis. All of them had a recent history of persistent albuminuria ranging from 1 plus to 4 plus in all specimens.
2. Eight patients with a common history of varied digestive disturbances involving myriads of complaints without definite implication of any specific disease entity.
3. Six patients with long-standing diabetes, all receiving 20–50 units of insulin daily and a routine low-carbohydrate moderate-protein diet.

Control total serum protein levels and A/G ratios were determined several times in each patient, and a general pattern of therapy was prescribed in an attempt to raise the serum protein levels.

The pre-established premise was that this entire group was in a state of mild to moderate protein depletion and negative nitrogen balance due to one or more factors involving inadequate protein intake or assimilation, pancreatic exocrine insufficiency, and/or inability to hydrolyze or utilize proper amounts of necessary proteins.

The intent was to correct diminished serum protein levels through 1) a high-protein diet, 2) administration of pepsin-pancreatin-bile salts[1] as replacement therapy, and 3) use of undenatured nucleoproteins in the form of brewer's yeast tablets, in order to enhance the proteolytic activity of the pancreatin and to provide various vitamins, ribonucleic acid and intrinsic factors.

Favorable results were ascertained by restoration of serum protein levels (particularly

[1] A mixture of pepsin-pancreatin-bile salts supplied as Entozyme through the courtesy of Doctor W. R. Bond of the A. H. Robins Company, Inc.

serum albumin) toward normal, and by diminution in the number and intensity of digestive complaints in the third group of patients.

The diet utilized was the modified Lowenstein (9) diet, consisting of not less than 120 Gm. per day of protein and not more than 45 Gm. per day of fats. Carbohydrates were adjusted individually according to the diabetic status of the patient.

Two Entozyme tablets were given with each meal, supplemented by 3 or 4 brewer's yeast tablets. A well balanced multivitamin capsule was added daily.

Every six to eight weeks, serum protein studies were repeated. Patients were also appraised for the degree of edema, albuminuria, and cardiac status. Diabetics were followed for alterations in insulin needs and the degree of hyperglycemia, glycosuria and acetonuria. Patients in the third group were examined and questioned at regular intervals concerning changes in symptomatology and general well-being.

Results

Figure 1 shows the curve of alterations in the level of serum protein in 24 of our 32 patients; these 24 adhered steadfastly to the prescribed regimen for a minimum of nine months; the remaining 8 interrupted their treatment schedule for three or more weeks and were dropped from the study.

The mean control level of total serum proteins was 6.95 Gm. per 100 ml. This value is slightly higher than those obtained by Chesrow (11); however, the average age of his patients was 78 years compared with an average age of slightly over 70 years in our group. The mean level of total serum proteins at the end of the investigation was 7.9 Gm. per 100 ml., an overall increase of about 14 per cent.

The mean control level of serum albumin was 4.46 Gm. per 100 ml., and the

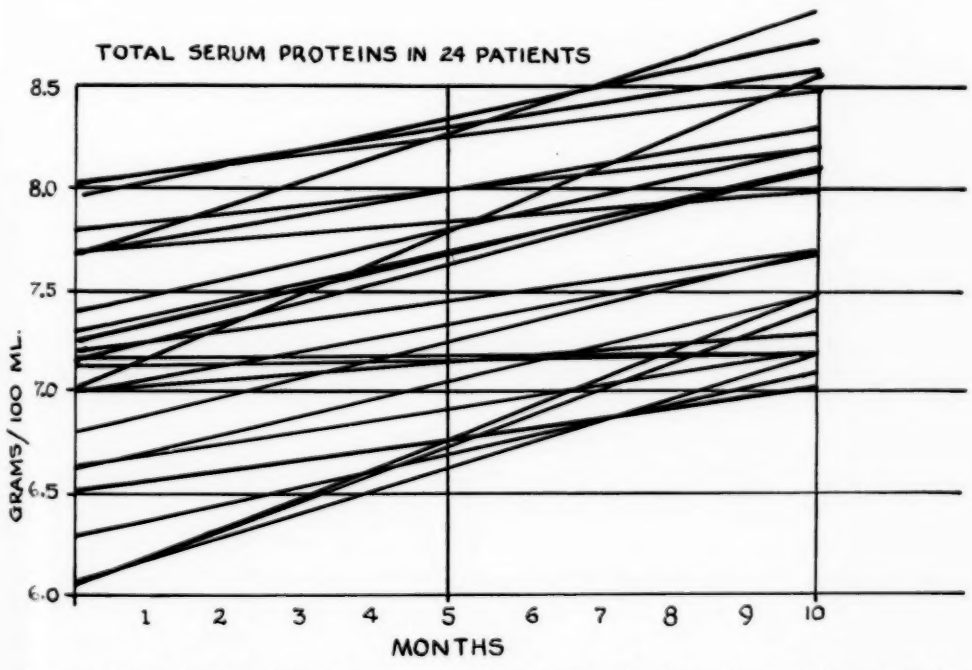

FIG. 1. Mean levels of total serum proteins in 24 geriatric patients before and after treatment with proteolytic enzyme supplements and a high-protein diet.

mean control level of serum globulin was 2.53 Gm. per 100 ml. At the conclusion of the study, the means were 4.73 Gm. for serum albumin and 3.0 Gm. for serum globulin, representing rises of 6 per cent and 9 per cent, respectively.

Clinically there was a noticeable decrease in peripheral edema in the patients with long-standing congestive heart failure, despite the fact that salt restriction and the intake of digitalis and diuretics remained unchanged. This was partly accounted for by the increased osmotic pressure of the serum.

Albuminuria persisted, but at a slightly lower level than before treatment. Apparently the renal lesions that resulted in the loss of albumin were not greatly affected by this regimen during the eight to ten months of the study period.

The second group of 8 patients, comprising those with complex and often unrelated histories of vague and disjointed digestive complaints, seemed to react well to the regimen. Complaints of "gas," bloatedness, and flatulence disappeared in 4 of the 8 and were diminished in 3 others. Anorexia, nausea, and heartburn were definitely ameliorated in 3 of the 8, and slightly in 3 others. Foul, frequent stools diminished in 3 of the 4 patients who had complained of them, and constipation was corrected in 2 of 4 others. Six of the 8 volunteered that they experienced a sense of energy and well-being; however, this report was regarded circumspectly due to the heavy psychosomatic overlay in their backgrounds lending an element of suggestibility whenever new medications were added to their treatment.

The six stabilized diabetics appeared clinically better in several respects. Improved muscle tone, increased energy, and higher resistance to intercurrent infections and upper respiratory disorders were noted. Three of the 6 patients were able to decrease their insulin dosage by 10 to 20 per cent without acetonuria. Serum cholesterol levels were diminished markedly in all 6, in some by as much as 30 to 40 per cent; here the lipotropic activity of adequate and more efficient protein metabolism became manifest.

COMMENT

One might speculate endlessly about the long-term benefits that might accrue in the field of degenerative diseases of the aged in association with a marked upswing in their utilization of protein. It is possible that the entire subject of atherogenesis might emerge from the area of heated disagreement if pancreatic insufficiency were given its proper niche in the larger pattern of lipotropic imbalances. The long-term complications of even controlled diabetes seem ready for explanation in the same area of physiologic interpretation. The indefinite digestive complaints of the geriatric patient in whom there is no clinical or laboratory evidence of a specific disease entity might finally yield to rational therapy. These are ripe fields for further thinking and clinical study. Since protein malnutrition may be the most significant factor in the etiology of many chronic diseases, it seems to be logical therapy to provide an adequate and qualitatively well balanced protein diet, as well as the enzymes for its proper digestion.

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TREATMENT OF NOCTURIA IN THE ELDERLY WITH POSTERIOR PITUITARY SNUFF

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Incontinence of urine or faeces is a distressingly common complaint. Brocklehurst (4) for example observed that 14 per cent of all patients in 5 Glasgow hospitals were afflicted in this way. Wilson (14) found that 25 out of 68 chronic sick patients over the age of 70 were incontinent of urine, 45 complained of frequency of micturition and 36 suffered from precipitancy. In fact, the majority of elderly persons, whether in hospital or not, are in the habit of rising at night to pass urine; inevitably many of them will become incontinent.

It is generally held that the principal cause of these symptoms, including incontinence, is failure of the cerebral cortex to inhibit premature contractions of a bladder which has become both hypertonic and hyperexcitable; moreover, the reduced capacity of such a bladder explains the small volumes of urine passed by old people. Another causative factor is diminution of renal concentrating power with advancing years, for lowered water resorption must necessarily result in an increased output of urine, especially during the night. Thirdly, there is a group of incontinent patients in whom dementia appears to account for the loss of control, rather than a local bladder disorder or polyuria.

In practice, the problem of incontinence of urine in the elderly has much in common with enuresis in the young. The therapeutic aim in both types of case is to restore control over micturition, regardless of whether symptoms be due to bladder dysfunction, polyuria or dementia. The success obtained in the treatment of diabetes insipidus with extracts of the posterior lobe of the pituitary gland led to the use of such an extract in the prevention of nocturnal enuresis in the young (2, 3, 5, 8, 10, 11). Since these clinical trials produced better results than those obtained by a variety of other methods it seemed logical to undertake a similar trial in the aged (1, 7). This paper describes the effects of posterior pituitary snuff on elderly patients suffering mainly from nocturnal frequency of micturition.

CLINICAL MATERIAL AND METHODS

Eleven elderly but cooperative subjects of both sexes were selected in 2 hospitals providing care for the chronically ill. All the patients chosen had been suffering from frequency, precipitancy, or occasional incontinence of urine for several weeks. Cases of neurological or neoplastic disease of the bladder and urinary tract were excluded from the trial, as were demented patients and those who were perpetually or doubly incontinent. Cases of moderate prostatic hypertrophy, cystocoele or prolapse of the uterus were accepted. Urinary infection

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was treated with appropriate drugs before evaluating the symptoms justifying snuff therapy.

Before starting treatment all patients were observed for at least two weeks; during this time fluids by mouth were forbidden after 6 p.m., the bladder was emptied at 9:30 p.m. (males standing), and for the next seven hours the night nurse recorded each act of micturition on a chart. The beds of those who were occasionally incontinent of urine were examined twice each night and the findings recorded. Patients who passed no urine between 9:30 p.m. and 4:30 a.m. were regarded as having had a "dry night."

Posterior pituitary snuff ("Di-sipidin") in gelatin capsules was administered by means of a specially designed insufflator. The dosage was increased weekly from an initial level of 1 capsule (containing 100 mg., equivalent to 30 anti-diuretic units) at 9:30 p.m., and another 1 or 2 capsules at 11:30 p.m., to a maximum of 5 capsules nightly. After continuous treatment for several weeks, most of the patients were kept under observation for a further period without snuff. Frequent estimations of the blood urea level were made during the period of hormone treatment.

CASE REPORTS AND RESULTS (TABLE 1)

Case 1. A male aged 81 was in good general condition but was suffering from prostatic enlargement. He had risen to pass urine at least thrice nightly for over sixty years. After two weeks of posterior pituitary snuff treatment (3 capsules nightly) he had 6 dry nights out of 7 for the first time in adult life. In the last week before transfer to the surgical department, capsules containing inert powder were used and the patient had to rise on 4 nights out of 7 to micturate.

Case 2. A female aged 78 was admitted for care and attention, and for treatment of an abscess in the right buttock. For many years she had risen to pass urine "5 or 6 times every night." After fluid restriction, nocturnal frequency was reduced to 9 times weekly, but when posterior pituitary snuff was given she had up to 2 dry nights out of 7 and only rarely had to rise more than once. The dosage in this case was 4 capsules in a single insufflation each night.

Case 3. A male aged 78 was helpless, confused, and suffering from right-sided hemiplegia. Incontinence of urine had occurred almost every night for several weeks. Posterior pituitary snuff was given for four weeks, beginning with a dosage of 1 capsule daily and increasing the amount weekly until the dosage was 4 capsules daily. In the last week incontinence occurred only once, and nocturia decreased slightly. Treatment was stopped because the patient required surgical treatment for obstructive jaundice.

Case 4. A male aged 70 years was in poor general condition owing to intermittent left ventricular failure, associated with hypertension (B.P. 210/130) and auricular fibrillation. A recent right-sided cerebral thrombosis had resulted in hemiplegia, and incontinence of urine occurred almost nightly. After assessment, 1 capsule of posterior pituitary snuff was given each night for two weeks, and then 2 capsules for a further week. No improvement in nocturia was noted; the patient's general condition rapidly deteriorated and the blood urea level rose to 61 mg. per 100 ml. The patient became demented and doubly incontinent.

Case 5. A female aged 76 had marked peripheral arteriosclerosis but her general condition was otherwise satisfactory and the urine was sterile. She was often incontinent of urine at night but sometimes used a bed-pan. Posterior pituitary snuff was given in a dosage of 1 capsule nightly for one week and then 2 capsules each night for a fortnight.

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TABLE 1

Results of Posterior Pituitary Snuff Treatment in 11 Cases of Nocturnal Frequency of Micturition

Patient		Duration of treatment (weeks)	Posterior pituitary snuff (maximum nightly dose in mg.)	Micturition (avge. No. of nightly acts per wk.)			Blood urea (range in mg./100 ml.)	Clinical results
Case No.	Sex, Age			Assessment period	During treatment	After treatment		
1	M81	4	300	9	3	4	30–38	Very good.
2	F78	9	400	9	6	6	38–24	Frequency reduced.
3	M78	4	400	6	4	not recorded	30–40	Frequency reduced; jaundice developed.
4	M70	3	200	6	6	not recorded	37–61	No improvement: demented and incontinent.
5	F76	3	200	6	2	not recorded	36–48	Immediate improvement.
6	F86	12	400	11	5	7	38–31	Frequency reduced; improvement maintained.
7	M64	11	400	7	8	9	36–31	No improvement.
8	M91	11	300	17	9	6	31–48	Progressive improvement.
9	M81	9	500	8	7	6	42–24	Slight improvement; frequent dry nights
10	F72	12	400	17	12	12	28–36	Frequency and incontinence diminished.
11	F74	10	500	18	18	17	39–46	No improvement.

In each of the second and third weeks of treatment the patient had 5 dry nights, but no subsequent records were kept.

Case 6. A female of 86 was bedridden because of advanced osteoarthritis. The blood pressure was 180/100. She had used a bed-pan three or four times every night for several years, but limitation of fluid reduced this to eleven times weekly. During treatment with 4 capsules of posterior pituitary snuff each night the patient had up to 5 dry nights in a week. After stopping treatment, her habit was to urinate once each night only.

Case 7. A male aged 64 was physically well except for signs of mild paraplegia. Treatment began with 2 dummy capsules for a week; no improvement resulted. Then 3 capsules of posterior pituitary snuff were given for a fortnight. For another nine weeks the patient received 4 capsules nightly without any obvious benefit. Later observations showed a slight increase in nocturnal frequency.

Case 8. A male aged 91 was a fit, alert old man whose habit had been to micturate four or five times each night over many years. Fluid restriction improved this to seventeen times weekly. When given 3 capsules of posterior pituitary snuff he had occasional dry nights; otherwise he urinated once or at the most twice each night and this improvement was maintained after treatment ceased.

Case 9. A male aged 81 was helpless and bedridden as a result of bilateral hemiplegia. Nocturnal urinary incontinence had been common, and initially posterior pituitary snuff therapy was unsuccessful. After six weeks of treatment, however, he had up to 4 dry nights per week; after four months, when snuff had been stopped, micturition was occurring on

only 6 out of 7 nights. In this case, 2 doses of snuff were given in the last fortnight of treatment—3 capsules at 9:30 p.m. and 2 capsules at 11:30 p.m.

Case 10. A female aged 72 years was bedridden because of severe osteoporosis and a spinal deformity. She occasionally wet the bed. Even after fluid restriction in the evening for two months, she continued to be troubled by nocturia. Treatment with 2 capsules of posterior pituitary snuff daily resulted in immediate improvement and incontinence diminished. Increases in dosage were made by adding 1, and then 2 further capsules at 11:30 p.m., and treatment was continued for seven weeks. Clinical improvement was maintained during and after this course of snuff.

Case 11. A female aged 74 was alert but somewhat uncooperative. She had been bedridden with advanced rheumatoid arthritis for two years. Her bladder capacity appeared to be no more than 4 ounces, and micturition occurred up to four times nightly. Fluids were restricted and records kept for one month before starting treatment; thereafter posterior pituitary snuff was given in increasing dosages up to 5 capsules (3 at 9:30 p.m. and 2 at 11:30 p.m.) daily. No improvement resulted and treatment was stopped because of an acute urinary infection.

Among these 11 patients, 8 experienced some reduction in the nightly frequency of micturition, and 5 of these were markedly improved. None, however, was cured and there were 3 failures—Cases 4, 7 and 11. The first of these failures was in a patient who was mentally confused at the onset of treatment and eventually became demented and doubly incontinent, necessitating transfer to a special unit. In Case 7 it was found subsequently that the patient was a mouth-breather at night; nasal obstruction was complete on one side due to a septal deflection and the other nostril was probably blocked by the insufflation of snuff. In Case 11 the patient resented all forms of treatment and was particularly thankful when snuff therapy ceased. With the exception of this last patient, the group as a whole felt well during treatment and most of them stated that they slept more soundly.

The blood urea concentration rose slightly during treatment in half the patients (Table 1). In 1 (Case 4) it reached a level of 61 mg. per 100 ml. in the third week.

DISCUSSION

Experimental work on diabetes insipidus has shown that the renal output of water is regulated by an antidiuretic hormone produced by the neurohypophysis (6). It is now recognized that the antidiuretic hormone is in fact vasopressin, to which the kidney is known to be extremely sensitive (12). In 1933 Klisiecki and associates (9) propounded the theory that the elimination of water by the kidneys was controlled by certain receptors which were influenced by the water content of the blood. It has since been shown by Verney (13) that vasopressin is liberated by the posterior lobe of the pituitary in response to stimulation of these osmoreceptors by a rise in the osmotic pressure of arterial blood. On the other hand, a rise in the water content of the blood suppresses the antidiuretic hormone and diuresis occurs.

In cases of frequency, precipitancy, or even frank incontinence of urine, treatment which aims at reducing the renal excretion of water seems logical. The

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use of antidiuretic hormone for this purpose does not imply that old people are deficient in this hormone, although without further study this possibility cannot be altogether denied. The results of this preliminary trial of hormone therapy showed that insufflations of posterior pituitary snuff relieved most patients of nocturia. It should be noted, however, that restriction of fluids in the evening invariably reduced the frequency of micturition during the night, an observation which suggests that release of vasopressin was still possible and that any deficiency of the hormone was at most relative.

From the practical point of view, posterior pituitary snuff is easily administered by the patient, a nurse or a relative. That it relieves symptoms in any degree makes it welcome to elderly persons. In this trial no obvious complications arose from its use, even after continuous administration for three months. It is difficult to know why treatment failed in some cases. The distribution of snuff over the nasal mucosa and the vascularity of this tissue are likely to have been variable factors; moreover, the influence of nephrosclerotic changes on the sensitivity of the kidney to antidiuretic hormone is not known, and it is possible that renal disease can vitiate the treatment. It has been shown that vasopressin is ineffective in certain cases of diabetes insipidus (6), and it is common experience that similar treatment of nocturnal enuresis is successful in only a proportion of patients, whether young or old. Nevertheless, the degree of success achieved in the present small group of elderly persons appears to justify an extended trial of this method, for any treatment which reduces nocturnal urinary symptoms will probably postpone the onset of incontinence.

SUMMARY

Posterior pituitary snuff (Di-sipidin) has been given to 11 patients suffering from frequency and precipitancy of micturition at night. There were 6 males and 5 females; the average ages were 78 and 77 years respectively.

Nocturnal frequency of micturition was reduced in 8 patients, 5 of whom were markedly improved. None was cured and there were 3 failures. No serious side-effects were observed.

The causes of frequency, precipitancy and incontinence of urine in the aged are discussed briefly and the mode of action of antidiuretic hormone on these symptoms is reviewed.

Acknowledgment

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HOST-TUMOR ANTAGONISM. XII. POSSIBLE EFFECT OF THE CORTISONE DRUGS ON THE DEVELOPMENT OF METASTASES IN PATIENTS WITH CARCINOMA*

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I. STATEMENT OF THE PROBLEM

Several cases of carcinoma have come to our attention in which it was felt that administration of cortisone or its derivatives for treatment of another ailment was associated with the development of metastases. This hypothesis cannot be proved in the human subject, since we do not know why cancers metastasize; all that can be said is that the development of metastases coincided in time with the use of the cortisone drugs. Others have noted this coincidence. For example, a report of the meeting of the Sub-committee on Steroids and Cancer which appeared in the *Journal of the American Medical Association* (1) contains the following statement:

"Cortisone and ACTH have been tested in terminal cases of various types of neoplasia. These agents allay pain and induce a sense of well-being, but do not alter the course of the disease. In several cases, despite the subjective response and the improved general condition of the patient, there was evidence of more rapid spread of the neoplasm, and autopsy later even revealed that the spleen had been riddled with metastases."

In an article by Shimkin and Moore (2), the statement appears, "Many investigators have noted that cortisone reduces host resistance, with resultant acceleration of tumor implantation and growth."

This latter statement refers to work in experimental animals and is extremely well documented. It is the purpose of this article 1) to review the animal work describing the effect of cortisone on the implanted tumor and the development of metastases, 2) to describe the possible ways in which metastases may be produced, and 3) to describe several patients in which the development of metastases coincided in time with the use of cortisone drugs.

II. ANIMAL STUDIES

The animal studies to be quoted are not strictly comparable to each other because of variability in the type of tumor, the animal used, the dosage of cortisone, and the time-relationship of the use of cortisone with induction of the

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tumor (whether used before induction, concurrently with it, or continued afterward). Nevertheless, the observations are better controlled than is possible in any patient.

Agosin and associates (3) showed that the local growth of transplantable adenocarcinoma K7 in C3H mice was arrested when cortisone was given. Metastases of this transplanted adenocarcinoma were never observed in untreated animals. However, metastases appeared in about five to six weeks following transplantation in animals treated with cortisone. The authors found that the longer the animals survived, the greater was the incidence of cortisone-induced metastases. These cortisone-induced metastases were transplantable, but produced only local growths from which metastases did not develop unless cortisone was given to the new host.

In a series of experiments, Christen, Agosin and Pizarro (4) attempted to determine the point of activity of cortisone. Cortisone was given before tumor transplantation in one series and was continued after tumor inoculation in another series, with the addition of suitable controls. Their results showed that 1) preliminary administration of cortisone allowed a greater growth of tumor than in the untreated animals, 2) in those animals in which the hormone was continued, the growth of the tumor was clearly inhibited, and 3) only in animals receiving cortisone did metastases develop.

In cortisone-treated animals there was a loss of 25 to 50 per cent of the weight of the adrenals and a loss of 50 to 75 per cent of the weight of the spleen, whereas in the untreated animals there was an increase of 10 per cent in weight of the adrenals and an increase of 400 per cent in weight of the spleen. The authors concluded that they could not determine the precise cause of the metastases.

Tallman and Gasic (5) noted that the mammary adenocarcinoma line K7 spontaneously acquired the capacity of producing metastases after the fifty-fifth passage, indicating that this property may depend on variations of the tumor cells themselves.

Duran-Reynals (6) found that cortisone caused inhibition of the primary growth of a chemically-induced transplantable tumor, but simultaneously caused the development of metastases and the provocation of a generalized infection by latent saprophytic bacteria. He commented that both the bacterium and cancer cell can be observed to be subject to the same influence, apparently following the same laws, and that the production of carcinomatous metastases may be likened to the formation of secondary abscesses in the course of septicemia, presumably subject to the same rules.

Baserga and Shubik (7) found that the effect of cortisone on the growth rate of induced tumors was variable. There was no inhibitory action on the growth rate of induced skin tumors or subcutaneously induced sarcomas. However, a temporary inhibition of the growth rate was noted in a transplanted mammary adenocarcinoma in DBA mice treated with cortisone. Such inhibition lasted for only ten days, after which the tumors actually grew faster. These authors also found that the induction of skin tumors in Swiss mice by methylcholanthrene was markedly inhibited by the administration of 0.5 mg. of cortisone daily.

More important, in common with other authors, they found that cortisone favored the metastatic spread of all the experimental tumors studied.

Engelbreth-Holm and Asboe-Hansen (8) reported a marked inhibition of experimental skin papilloma in mice induced by a single painting with 9,10-dimethyl-1,2-benzanthrene and subsequent treatment of the mice with cortisone for eight weeks. Boutwell and Rusch (9) found that cortisone had no effect on the induction of carcinoma by benzpyrene. However, the results of studies on the development of papilloma were in great contrast. In only 5 per cent of the mice given cortisone orally and 19 per cent of the mice treated locally with cortisone did papillomas develop, whereas these tumors were found in 50 per cent of the mice not given cortisone.

Kaliss and Snell (10) worked along the lines that lyophilized cancer from the strain indigenous to the cancer graft enhances the growth of the homeograft in the strain so treated, which ordinarily will not grow the graft. Kaliss and Molomut (11) noted that this phenomenon also occurs with antiserum to the tissues prepared in either rabbits or mice.

Molomut and co-workers (12) found that mice given lyophilized sarcoma I followed by a live implant one week later, and treated with cortisone, showed widespread metastases. No metastases developed in the control mice given lyophilized sarcoma I and then a live implant.

Contradictory results have been obtained concerning the effects of cortisone in mice. Both a lowered incidence and an increased incidence have been reported in the literature. Spain, Molomut and Novikoff (13) believe that these differences may be due to variations in the experimental procedure, such as the strain of mice, the dosage of cortisone, the nature of the carcinogen, and the duration of treatment with cortisone. In an experimental study, these authors concluded that the administration of cortisone increased the incidence of skin tumors in mice that received multiple paintings with methylcholanthrene. This enhancement occurred even when cortisone was administered during the early phase of the carcinogenic process. Cortisone treatment did not result in the development of metastases from the methylcholanthrene-induced carcinomas.

In another interesting series of experiments. Molomut and co-workers (12) attempted to determine what effect wounding, used as a traumatic stimulus, would have on the growth of an homologous cancer graft. Wounding consisted of opening a wound surgically each day in order to mimic the situation of continuously granulating tissue. They concluded that the maintenance of an active inflammatory response in the local tumor site acts to "contain" an homologous cancer graft, which grows more slowly than in normal mice.

III. ILLUSTRATIVE CASE REPORTS

Case 1

A. G., a 56-year-old woman, stated that she had noted a lump under her right arm in August 1955. She underwent a right radical mastectomy in September 1955 for carcinoma of the breast with metastases to the axillary nodes. She received postoperative x-ray therapy to the chest area. In November 1955, x-ray survey showed widespread metastases to the bones. In December 1955, injections of androgen (Stanolone) were started, and

continued to the present (July 1957), although irregularly in recent months. She felt well until May 1957, when she noted buzzing in the left ear which persisted and increased. In addition, she noticed impaired hearing in her left ear. More recently she also noted constant machinery-like noise in the right ear. Puffiness under the eyes had been present for one and a half months, at the time of admission. She had not complained of headache, and in general, felt quite well.

Her past history revealed that she had toxemia of pregnancy twenty-eight years previously. She stated that she had some congenital type of kidney disorder most of her life, but that it had not been bothersome. She had no urinary symptoms, but it had been noted that she had albumin in the urine. She had undergone a hysterectomy nine years previously, for fibroids, at which time both ovaries had been removed. The remainder of her history was not contributory.

Physical examination revealed a well-developed and nourished woman with prominent veins on the forehead. There was considerable puffiness beneath the eyes. No thrill or bruit was audible in the skull. Funduscopic examination showed moderate choking of the right disc; the left disc appeared normal. There was no hemorrhage or exudate. Both eardrums were intact and air conduction was greater than bone conduction in both ears, although there appeared to be some impairment of hearing in the left ear. There were multiple small cutaneous nodules in the neck, chest wall and axilla, which appeared to be metastatic and of recent origin. The left breast was normal. The heart and lungs and abdomen were also normal. Blood pressure was 160/100. The reflexes were equal but somewhat hyperactive; no pathologic reflexes were obtained.

X-ray examination of the chest and skeleton on July 3, 1957, showed that there had been a remarkable recalcification of the widespread, fine osteolytic metastases throughout the skull, spine and pelvis noted in November 1955.

X-ray therapy to the skull was advised and carried out. In addition prednisone was given in a dosage of 5 mg. four times daily. Within a week a low-grade fever (100.6° to 101°) and many new cutaneous metastases developed. In addition, exophthalmos appeared on the right, undoubtedly due to additional intracerebral metastases. Prednisone was continued, and antibiotics were given, although no infectious cause for the fever could be found. The right-sided exophthalmos increased, and there was some suggestion of exophthalmos on the left. More nodules became visible in the skin. Prednisone was withdrawn, and within a few days the fever disappeared. The rapid growth of the cutaneous nodules was slowed, but they did not disappear. The exophthalmos remained. The patient died on January 15, 1958, after a slow progression of the cerebral and cutaneous lesions.

Case 2

M. F., a woman aged 60, was first seen on August 15, 1956 with pains in the groin and back. Two weeks before there had been pain in the right shoulder and elbow, and there was still some redness and heat in the right elbow. The pain in the groin was due to acute arthritis of the right hip joint. For the previous year, the patient had complained of hoarseness, for which she had visited a laryngologist. Upon inquiry, the laryngologist told us that he had diagnosed the ailment as chronic laryngitis. He stated that the patient definitely had not had a tumor of the larynx.

The hematologic report on August 15, 1956, showed the following: hemoglobin level 10.4 Gm. per 100 ml.; erythrocyte count, 3.7 million per cu. mm.; leukocyte count, 12,200 per cu. mm., with 68 per cent polymorphonuclear cells, 2 per cent eosinophils, 26 per cent lymphocytes, and 4 per cent monocytes. The sedimentation rate was 30 mm. per hour (Wintrobe, 2–20 mm. normal for females).

Prednisolone (5 mg. four times daily) was prescribed for the acute arthritis.

On September 19, 1956, the joint symptoms had improved, the patient had gained weight, but the sedimentation rate was 35 mm. per hour. The erythrocyte count was 4.6 million per cu. mm. and the hemoglobin level was 13.8 Gm. per 100 ml. The hoarseness was still present. Prednisolone was continued.

On October 31, 1956, she complained of severe cough, high fever (104°) and increasing hoarseness. She was hospitalized. The laryngologist found a carcinoma of the larynx. In addition, she had metastases to the lung, liver and skin. Metastases from carcinoma of the larynx are usually not found under ordinary circumstances. The patient died on January 15, 1957 of multiple metastases.

Case 3

J. K., a woman aged 49, was first seen on January 2, 1957. A small, hard nodule was noted in her right breast. There were no axillary metastases. She was hospitalized immediately, and a simple mastectomy was performed. A bilateral oophorectomy was carried out several days later. About four weeks after leaving the hospital, she received 30 radiation treatments. She progressed satisfactorily for several months, and felt strong enough to take full charge of her household.

On July 5, 1957 she complained of pain and tightness in her neck. The entire thyroid gland was enlarged and very tender. A diagnosis of acute thyroiditis was made, and prednisolone was given in a dosage of 5 mg. three times daily. The tenderness of the thyroid diminished in about one week, and the gland appeared slightly smaller. Prednisolone was continued for an additional two weeks in half the dosage, after which it was stopped because the gland had become normal size.

On September 15, 1957 she complained of new pain in the right hip and thigh. It was diagnosed as due to arthritis of the hip, and prednisolone (5 mg. four times daily) was given. Soon, however, there was tenderness over several ribs on the right side, and x-ray examination showed involvement of the ribs, pelvis and right femur. With androgen (Stanolone) therapy the pain subsided somewhat, but more and more metastases occurred. The patient died on December 26, 1957.

Case 4

H. E., a man aged 63, had carcinoma of the left colon. In 1949 resection of the colon and one lymph node was performed. There was no evidence of disease in the summer of 1952. In September 1952, bursitis of the shoulder developed, and cortisone was given by mouth. Within three weeks, a colonic mass the size of a grapefruit and liver metastases were noted. The patient could not stand up because of pain and loss of weight. Coley's toxins were given aggressively for about four weeks intravenously. There was complete regression of the mass within this time, and the liver decreased in size also. Simultaneously, acute polyarthritis developed. The joints were very painful. Coley's toxins were stopped and the patient was given cortisone for arthritis. Immediately, he felt much worse. He died of multiple pulmonary and abdominal metastases in the fall of 1953.

IV. DISCUSSION

Unfortunately, we do not know why cancers metastasize. The classical concept is that invasiveness of the cancer is dependent upon certain physical changes in the area surrounding the cancer cell, and this will be discussed in detail. The finding of metastases in these 4 patients during, or soon after treatment with cortisone or its products may be purely coincidental. However, the results of animal experiments are not so controversial.

Most of the animal experiments have indicated that cortisone causes a suppression of the primary tumor growth with the concomitant development of metastases. The effect persisted only in treated animals, and grafting of the metastatic tissue induced only an ordinary tumor without any tendency to metastasize. Moreover, the effect on the primary tumor existed only as long as the hormone was given, and there was no sign of suppression after cortisone was

discontinued. These facts speak for an indirect, rather than a direct action of cortisone on the tumor cells. One of these indirect mechanisms may be through the lymphatic depletion effect of cortisone. This theory has been held for years, and its most vigorous proponent was Murphy (14). The lymphocyte is considered at present to be the source of antibody. Thus if "tumor immunity" exists, it may be depleted by the effect of cortisone on the lymphocyte.

Another possible manner in which cortisone may act is through its effect on the connective tissue throughout the body. Since this is one of the principal actions of cortisone, it will be discussed in some detail later.

Duran-Reynals (6) noted inhibition of primary tumor growth with simultaneous induction of metastases, and the development of generalized infection by latent saprophytic bacteria, in cortisone-treated mice. The parallel behavior of bacteria and cancer cells can be further demonstrated by the apparently antagonistic effect of estrone. This hormone has the property of stimulating the formation of large amounts of ground substance in monkeys and mice. Estrone strongly protects against streptococcal, pneumococcal and tubercular infection, and also strongly inhibits the growth of transplantable tumors in animals. According to Duran-Reynals, the action of estrone in inhibiting infection is due in large measure to its effect on the ground substance, and he felt that he had strong evidence for the same mechanism in cancer. Thus the effect of hormones on the ground substance and other elements of the connective tissue of both tumor and host may be of unique importance.

An attractive possibility in the explanation of metastases is based on the fact that cancer tissue contains a large concentration of a mucolytic enzyme, and that appropriate substrate materials on which such an enzyme may act are present in the ground substance of connective tissue (15). Although hyaluronidase production is probably not the basis of invasive growth, it is possible that some other mucolytic enzyme secreted by cancer cells may open the way to invasion of adjacent tissue. Coman (16) believed that invasiveness is dependent upon physical changes in the area surrounding the cancer cells. These differing views will be discussed.

a) *The classical concepts of the origin and dissemination of metastases*

Based on a great deal of experimental evidence, Coman (16) elucidated his concepts of the origin and dissemination of metastases. He felt that the local invasiveness of cancer cells is primarily dependent upon loss of mutual adhesiveness of the cells, and that this loss is associated with a local deficiency of calcium. The easily detached cancer cells possess ameboid motility and can thereby penetrate adjacent local tissues.

Following local invasiveness, distal dissemination is largely dependent upon the entrance of cells into vascular channels through which they are carried to other parts of the body. Many of these embolic cells are unable to establish secondary growths in their new location. Coman felt that duration of the growth, rather than its size, bears the more important relationship to the number of metastases, and that the venous distribution of metastases is dependent upon

the anatomic arrangement of the venous channels, especially the vertebral veins. This accounts for the frequency of metastases to the lungs, liver, spine, pelvic bones and skull. When considering the arterial distribution, the development of metastases depends not only upon the number of embolic cells that reach the various organs, but also upon whether the cancer cells land in capillaries and sinusoids or in thick-walled arterioles. Tumor cells lodging in arterioles frequently do not survive, in contrast to those that lodge in capillaries and thin-walled veins. This may account for the relative infrequency of metastases to the spleen and muscle, and the frequency of metastases to other organs such as the adrenal or kidney. Although the lungs are frequently the site of metastatic tumors, because of their peculiar physical structure they afford relatively adverse conditions for tumor growth. Coman felt that transpulmonary passage of embolic tumors cells occurs relatively often, and that single embolic cells or small clusters give rise to most metastases, because these cells are able to reach the capillary bed where conditions are the most favorable for growth.

Coman also concluded that the hypothetical "chemical soil" factors in the distribution of metastatic tumors are really physical or mechanical differences in the circulatory system.

b) *Possibility of dissemination of cancer through alteration of connective tissue by cortisone*

Since cortisone has a marked effect on connective tissue, it was thought worthwhile to review the literature on this structure and note the effects of cortisone on its components (17).

Connective tissue, a derivative of the mesenchyme is the most widespread structure in the body. It comprises fascia, tendons, joint capsules, the major portion of the skin, important parts of the heart and blood vessels, the loose interstitial connective tissue, cartilage and the bones. Adipose tissue is a specialized variant of connective tissue, and is also part of the reticulo-endothelial system. Even the cells of the circulating blood are derived from the mesenchymal stem cells in the bone marrow. The cavities of the joints and the eyeball are mesenchymal spaces, and these spaces are filled with a mucinous substance, the composition of which resembles closely that of the ground substance of connective tissue.

Connective tissue is made up of cells and intercellular substances. The intercellular, or ground substance, ensheathes the individual fibrils and forms the intercellular cement; it varies greatly in the different organs. In hyaline cartilage it has a firm rubber-like consistency, and in bone it appears as deposits of calcium salts. The ground substance contains salt and water, protein, sugars and mucopolysaccharides. Among the mucopolysaccharides are hyaluronic acid and chondroitin sulfuric acid.

The fibrous elements in the ground substance are in 3 groups, namely, collagenous fibers, elastic fibers and reticulin fibers.

The cells of the connective tissue are the fibroblasts (or their variants, osteocytes and chondrocytes), mast cells and wandering cells, which include the

macrophages. The fibroblasts are the most common cells. Their main role appears to be the formation of collagen, which is liberated into the intercellular space and subsequently polymerized to form collagenous fibrils. Mast cells are large and contain globular cytoplasmic granules which stain metachromatically with various basic dyes. The granules contain acid mucopolysaccharides which may be liberated into the ground substance. The granular substance probably contains a precursor of hyaluronic acid and heparin. In addition, the mast cell synthesizes histamine and contains serotonin in some species.

Reticuloendothelial cells are present in the spleen, liver, bone marrow and loose connective tissue. These cells engulf cellular debris, bacteria and foreign matter, and play an important role in antibody formation.

Many hormones produce profound changes in the structure of connective tissue. Among the most important changes are those produced by corticotropin (ACTH) and the adrenocortical hormones. Thyroid hormone and the sex hormones also have pronounced effects on connective tissue components.

Administration of corticotropin, cortisone or hydrocortisone affects the structure of the mast cells, which diminish in number, become vacuolated and irregular in outline. Where the mast cells undergo structural alterations following administration of cortisone, the metachromatic staining of the ground substance is reduced. Cortisone inhibits the synthesis of chondroitin sulfuric acid in connective-tissue ground substance, and reduces the spreading capacity of hyaluronidase in the skin of rabbits and human subjects. In experimental skin wounds of rabbits treated with cortisone, there is a reduced count of fibroblasts. Cortisone inhibits intracellular digestion of bacteria in macrophages, inhibits the regeneration of the reticuloendothelial system after it has been blocked, and reduces the lymphocyte, basophil, and eosinophil counts in peripheral blood. Thus administration of cortisone can cause such marked alterations in connective tissue, which is widely dispersed throughout the body, that it may possibly favor metastasis on this basis.

c) *Possibility of dissemination of cancer through depletion of lymphoid tissue by cortisone*

Toolan (18) reported that he was able to grow human tumors in rats that had received x-ray radiation or cortisone—forms of therapy which may work through the depletion of lymphatic structures. X-ray radiation and cortisone, therefore, are alike in inhibiting the mechanism concerned with heteroplastic tissue transplants.

Previously, Murphy (14) showed experimentally that the lymphoid elements of the body are important in cancer immunity. By studying the natural progress in a tumor transplant he found that, in a resistant host, there was local round-cell infiltration about the graft. The local reaction was accompanied by a marked increase in circulating mononuclear cells, and by an increased proliferation of the lymphogenic centers. In a susceptible host that supported a growing tumor, the lymphoid tissue underwent marked degenerative changes. Murphy demonstrated that experimentally-produced variation in the amount and activity of

lymphoid tissue is correlated with variation in the resistance of the animal to cancer. He felt that the response of lymphoid tissue to a cancer transplant is a general reaction, even though there is a high degree of local resistance when sufficient local lymphoid reaction is induced.

Murphy showed that doses of x-ray radiation sufficient to deplete the lymphoid system, lowered the resistance of mice to tumor transplants. He questioned whether intensive x-ray therapy in man may not interfere with the defensive mechanisms, *e.g.*, tumor immunity. In trying to explain why x-ray therapy of skin cancer is so effective, he pointed out that the dosage of radiation in these circumstances is applied over too small an area to have any effect on resistance. He believed that x-ray therapy confers a local immunity to the skin area and makes it an unsuitable soil for tumor growth. This refractory state is confined to the layers of the skin, and does not even extend to the underlying connective tissue. Thus, the therapeutic value of x-ray radiation in cancer depends upon the cellular reaction of the normal tissues surrounding the neoplasm. Murphy demonstrated this by an ingenious experiment with spontaneous cancers in mice. Skin cancers disappeared promptly after a mild erythema dose of x-rays, but when, after exposure, the tumor was removed and replanted in the same animal in an untreated area, the neoplasm would grow as if no treatment had been given. Conversely, when a graft was implanted in an area previously treated by x-rays, degenerative changes occurred in the cancer cells, even though they themselves had not been treated.

d) *The effect of cortisone and other agents on the production of tumors following injection of a virus*

Duran-Reynals (19) showed experimentally that viruses which under ordinary circumstances induce immediate, inflammatory lesions that end in necrosis, can start or cause neoplastic and malignant lesions under other conditions. These conditions include administration of methylcholanthrene and treatment with cortisone. Cortisone depletes the mesenchyme and its ground substance which may play an important role in destroying viruses. Estrogen, however, produces a marked increase of dermal ground substance.

The intradermal injection of a suspension of vaccine virus from infected rabbit testes into Swiss mice prepared by skin paintings with methylcholanthrene combined with injection of cortisone result in the development of a greatly enhanced dermal infection. In many animals, this was followed by the development of a variety of both benign and malignant neoplastic lesions arising strictly from the precise site (identified by the scar) where the virus material was injected. Such neoplastic lesions never developed following injection of the virus suspension into mice prepared 1) only with methylcholanthrene, 2) only with cortisone, 3) with estrogen, with or without methylcholanthrene. In the second group the infection was enhanced but in the third group it was suppressed.

Duran-Reynals concluded that subsequent to an acute virus infection, tumors arose at the precise site of the virus lesions only in mice prepared with methylcholanthrene and cortisone.

e) *Does "tumor immunity" exist?*

Although the arguments for and against this possibility have formed the subject matter of several essays in this series, the question still cannot be answered. Most of the evidence is circumstantial and inferential. The animal work dating from the pioneer studies of Gaylord and Clowes (20), Lumsden (21), and more recently M. R. Lewis and her associates (22), is the most convincing, so far. However, many animal tumors have been proved to be virus-induced, and we would expect some sort of immunity to this type of affection. There is no direct evidence at this time that human tumors are virus-induced.

Makari (23) demonstrated that the blood serum of patients with cancer contains a specific antigen. The Grahams (24) also found antibodies in human subjects with carcinoma, by the complement fixation technique. They used the patient's tumor as antigen and the patient's serum as the source of antibodies. In 12 of 48 subjects there were significant titers, ranging from 1:16 to 1:128.

It may be questioned how an immune reaction can be established in an organism, when the neoplasm originates from the host tissues and is therefore indigenous to the host. The answer to this question undoubtedly is that the neoplasm represents a slight difference or mutation from the host tissues, perhaps only so much as a loss or gain of a few enzyme systems. However, the immune mechanisms of cancer patients are at such a low ebb that they may be in a state of immunologic paralysis with respect to cancer.

Southam, Moore and Rhoads (25) reported significant information on the defense mechanisms of the normal human body against implanted cancers. Implants of human cancer were made in healthy prisoner-volunteers and in patient-volunteers with far advanced cancer. In 13 of 15 cancer patients, the cancer implants grew until they were removed one to six weeks later. In 4 of the cancer patients the tumors recurred even after the implants had been carefully removed. In the group of healthy volunteers, there was a vigorous local reaction to the cancer implants and all the cancer cells were destroyed by the end of two weeks. When these same normal volunteers were reinoculated with the same type of cancer cells that they had received previously, it was found that the cancer cells were destroyed more rapidly than before.

In another study, inmates who had earlier received implants of one type of cancer cell, received implants of a different type of cancer cell. The latter cells were destroyed more rapidly than those given initially, but less efficiently than a second implant of the same cells.

Southam, Moore and Rhoads studied the blood of both the cancer patients and the healthy volunteers in order to find the factors involved in the reaction to cancer implants. Although the cancer patients lacked definite mechanisms against implanted cancer cells, they were not deficient in lymphocytes or in the ability to produce an inflammatory response to irritants or bacterial infections. However, the amount of properdin in their blood was less than in the blood of the healthy subjects. The level of properdin could be considered as representative of the state of the general body defenses, but it was thought that there must also be a specific defense mechanism against implanted cancer. This was implied in

the more vigorous reactions of the healthy volunteers to the second and third implants. So far, these investigators have not found any serum antibodies to implanted cancers.

SUMMARY AND CONCLUSIONS

The possibility exists that cortisone or its derivatives given to a patient who has been operated on for cancer may cause dissemination of the growth.

Animal experiments which bear out this possibility are described.

Four patients are discussed, in whom widespread metastases occurred in association with treatment by cortisone drugs.

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CHEMOSURGERY FOR BRAIN TUMOR: A PRELIMINARY REPORT*

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It is the purpose of this preliminary report to call attention to a new approach to the treatment of infiltrating tumors deep within the brain. Brain tumors of this type have been generally considered inoperable because of 1) their infiltrating characteristics, 2) their inaccessible position with the brain, and 3) their tendency to invade the basal ganglia. Classic surgical attempts to reach these deep tumors by way of extensive craniotomy and incisions through the brain have usually met with extremely limited success, even as regards palliation.

A successful operation for this type of tumor, from either a palliative or a definitive therapeutic standpoint, should have certain fundamental attributes: 1) The tumor should be destroyed from within itself, in order to avoid damage to the surrounding brain structure. 2) Destruction should be gradual, so that as normal brain structure is approached, the degree of destruction can be lessened, thereby reducing the danger to the patient's neurologic and psychologic functioning. 3) The operation should be performed on a conscious cooperative patient whose condition will be a guide to the surgeon in his efforts to avoid damage to the patient's functional ability. 4). The technique should involve some method of visualizing the rate and extent of destruction of the tumor.

NEW SURGICAL TECHNIQUE

A surgical procedure has been devised for the treatment of deep, infiltrating brain tumors, which appears to fulfill the foregoing criteria. It has been derived from the techniques of chemopallidectomy and chemothalamectomy, whereby a lesion can be produced gradually, deep within the basal ganglia, by way of a dime-sized trephine opening in the skull in a conscious cooperative patient; at the same time the surgeon is able to follow the progress of this lesion (which is radio-opaque) by means of roentgenograms.

At the present time, the position of a deeply situated intracerebral tumor can be gauged accurately in most cases by the use of air contrast studies combined with arteriography. Once this is done, it is a relatively simple procedure to place a specially devised cannula into the tumor through a small (less than 2 cm. diameter) opening in the skull. When it has been verified roentgenographically that the tip of the cannula is in the tumor mass, a small balloon is distended

* This study was assisted by grants from the Sister Kenny Foundation and the Allan P. & Josephine B. Green Foundation.

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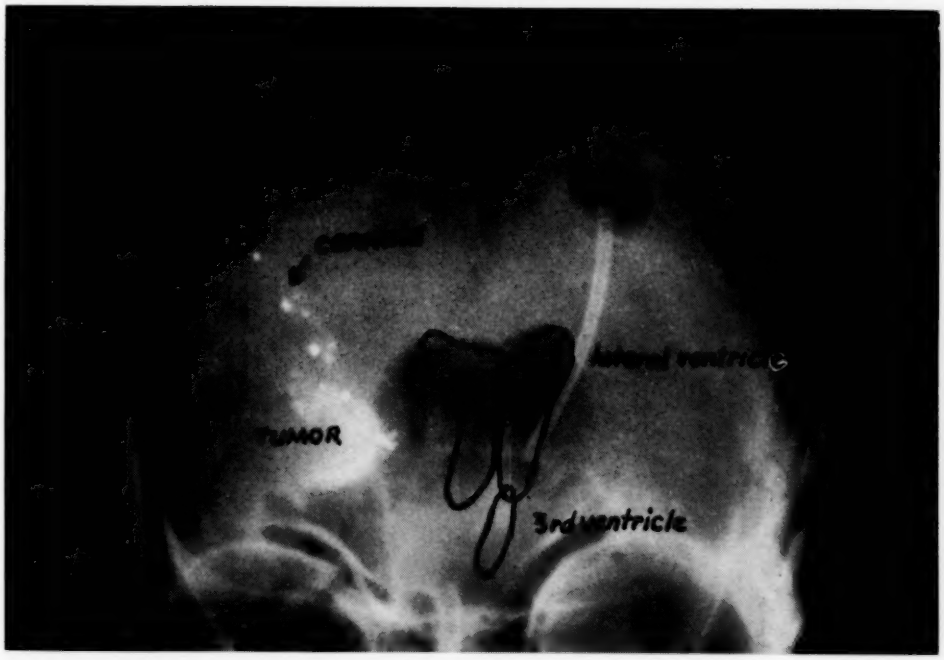

FIG. 1. Roentgenogram demonstrating tumor stained by technique of chemosurgery described in this publication.

within it in order to provide a cavity to receive the subsequent injection of the neurolytic, fixative or tumoricidal agent directly within the tumor. Through this properly positioned cannula, a combination of absolute alcohol and Pantopaque or of phenol and Pantopaque, is gradually introduced. By means of serial injections of increasing amounts, the area of destruction can be enlarged in concentric spheres, so that the surgeon literally destroys the tumor from within itself. Tumor debris can be withdrawn through the cannula.

During the series of injections, the brain cannula is allowed to remain in its intracerebral position for several days. The accuracy and efficacy of the treatment may be checked as follows: 1) The state of the conscious patient is a guide to the neurologic and psychologic effects of the injections. 2) Since the neurolytic or tumoricidal agent is stained with Pantopaque, the extent of tissue destruction can be checked roentgenographically, as shown in Figure 1. 3) Serial pneumoencephalography, ventriculography and arteriography may be employed to aid in the estimation of the tumor's position and size, as well as the status of neighboring cerebral structures.

This procedure for cannula placement may be performed under local anesthesia with a minimum of risk or morbidity. It offers a method for palliative, and occasionally for definitive, surgical treatment of deep cerebral neoplasms. At the present time it is being used as an investigative technique on our service, and therefore is limited to cases which are otherwise inoperable. However, this type of tumor surgery, in which destruction is commenced within the tumor itself, may prove to be applicable in a much wider range of cases.

SUMMARY

A preliminary report is presented of a new approach to the surgical destruction of deep, infiltrating cerebral tumors. The method has the following advantages: 1) It is simple and can be performed through a dime-sized trephine opening under local anesthesia. 2) It involves accurate placement of a brain cannula within the center of the deep-lying tumor, and thus permits destruction of the neoplasm from within itself. 3) Destruction of the tumor from within, safeguards the surrounding normal cerebral structures. 4) The neurolytic or tumoricidal agent is injected gradually in a conscious cooperative patient, thus reducing the risk of damage to the patient's neurologic function. 5) Since the neurolytic agent is stained with a radio-opaque dye, the rate and extent of tissue destruction can be estimated roentgenographically. 6) Additional checks on the progress of tumor destruction may be made by means of serial ventriculograms, pneumoencephalograms and arteriograms.

NEUROSURGICAL RELIEF OF INTENTION (CEREBELLAR) TREMOR.

A Preliminary Report*

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During the past six years we have carried out more than 1000 basal ganglia operations for the relief of resting parkinsonian tremor, rigidity, dystonia and other involuntary movements. The principal involuntary movement which we have studied in this series was the resting tremor of parkinsonism. This particular tremor, which is present when the involved extremity is at rest, often disappears when the extremity performs a voluntary motor act. The fact that resting parkinsonian tremor can be relieved by surgery of the basal ganglia, and that such relief has endured for more than six years in our earlier cases, has been documented in earlier reports (1).

It is generally agreed that the tremor seen in cerebellar degenerative diseases, in some cases of cerebellar tumor, and in multiple sclerosis is different from the tremor of parkinsonism. Cerebellar tremor is usually not present when the involved extremity is at rest, but appears only when the extremity is used for a voluntary motor act, such as lifting a glass of water, attempting to write, or performing other purposeful movements. The classic clinical test for this type of tremor is the finger-to-nose maneuver, in which the tremor appears in the patient's index finger as it approaches his nose, and becomes violent in the final effort to place the end of the finger upon the tip of the nose. This tremor is not relieved by medications, and has usually been refractory to any form of therapy.

A recent development holds promise for eventual understanding of the mechanism of intention tremor, as well as for its therapeutic alleviation. In the course of our 1000+ basal ganglia operations for parkinsonism, we observed that in some of the more severe cases, both intention tremor and resting tremor were present, and that both types of tremor were relieved by chemothalamectomy, which is now our procedure of choice for the treatment of parkinsonism. We therefore selected several cases of severe intention tremor (appearing only during voluntary motion of the extremities) for chemothalamectomy.

It is the purpose of this preliminary report to point out the beneficial results of chemothalamectomy in the treatment of pure intention tremor. In our parkinsonian tremor series, we were able to present six-year follow-up studies of cases in which there had been no recurrence. In the intention (cerebellar) tremor

* This study was assisted by grants from the Sister Kenny Foundation and the Allan P. & Josephine B. Green Foundation.

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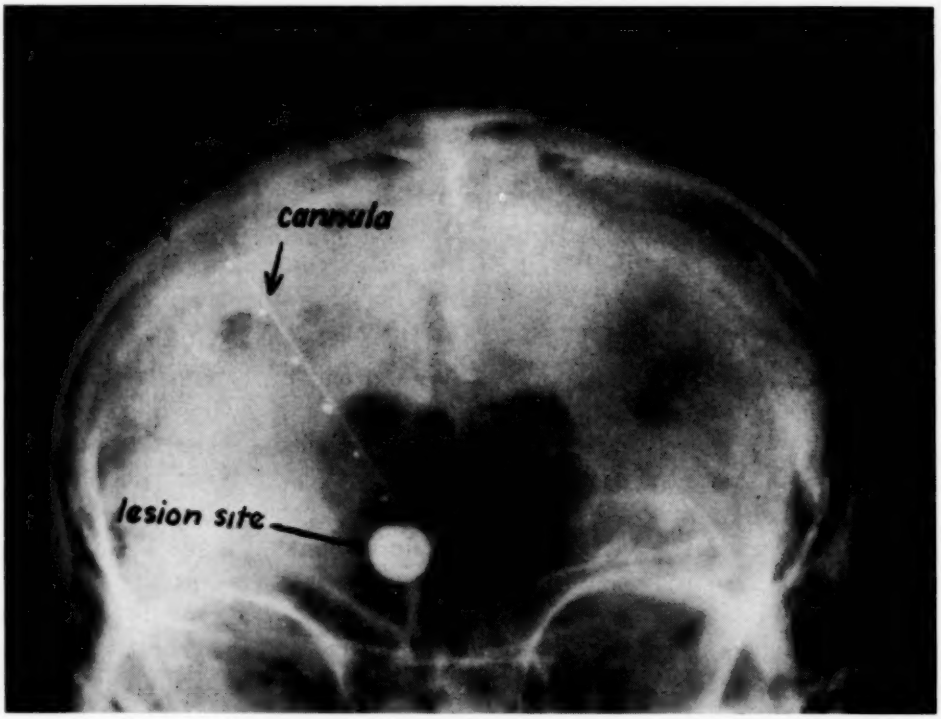

FIG. 1. Roentgenogram demonstrating inflated balloon within the brain of a patient with intention tremor. Inflation of the balloon at this site produced immediate cessation of the tremor.

series, our experience to date is limited to a six-month follow-up of cases without recurrence.

Figures 1 and 2 demonstrate the lesion employed to alleviate intention (cerebellar) tremor. Placed in the thalamus, it interrupts nerve fibers entering the thalamus from the globus pallidus, red nucleus and cerebellum. Probably the vestibulo-thalamic fibers are also interrupted. The fact that so-called cerebellar tremor can be alleviated by interrupting the fibers of the cerebellar system may at first seem surprising. However, it should be borne in mind that it has been proved beyond question that parkinsonian tremor, generally acknowledged to be a basal ganglia phenomenon, is consistently relieved by basal ganglia surgery. Considerable evidence has accumulated in the course of physiologic operations upon the central nervous system which indicates that a partially damaged system may produce more abnormal symptoms than a totally damaged system, particularly if compensating mechanisms exist in one or both cerebral hemispheres.

SUMMARY

Intention (cerebellar) tremor may be relieved by chemothalamectomy, a lesion produced in the medial portion of the lateroventral nucleus of the thalamus. This lesion interrupts nerve fibers entering the thalamus from the globus pallidus,

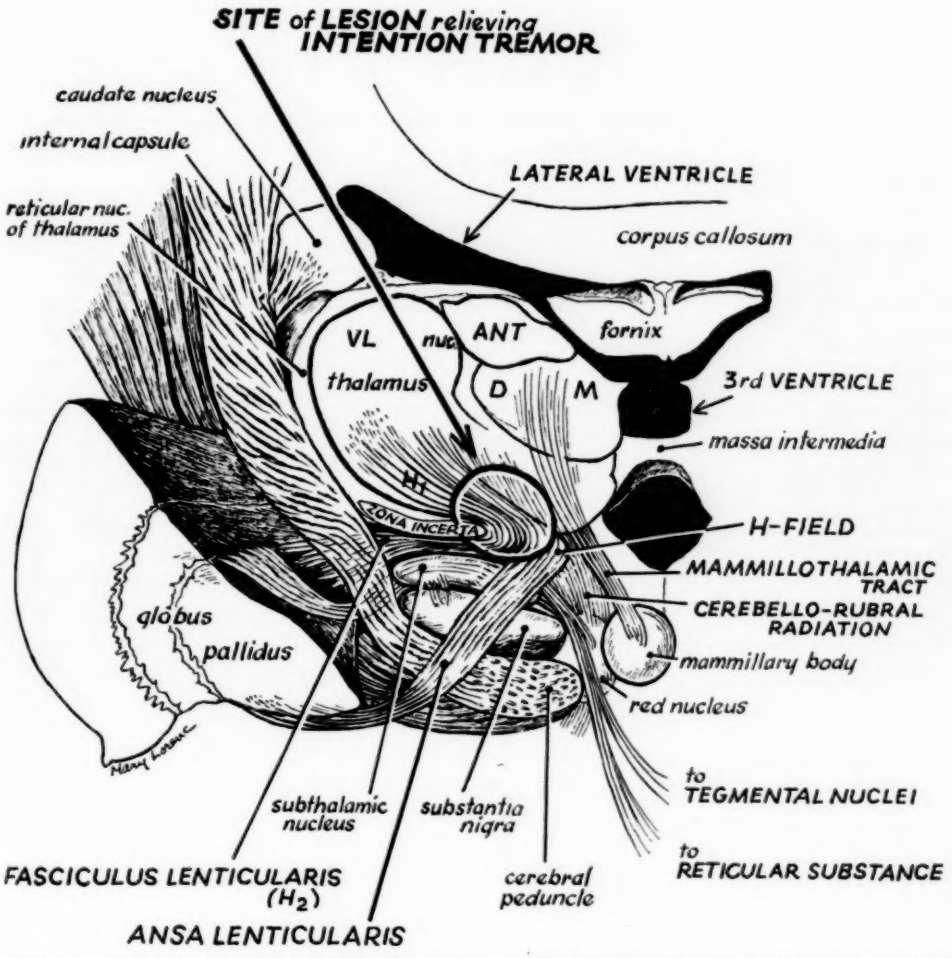

FIG. 2. Anatomic interpretation of the lesion which has alleviated intention tremor. This lesion interrupts pathways to the thalamus via the fasciculus lenticularis, ansa lenticularis, red nucleus and cerebellum.

red nucleus, cerebellum, and probably also the vestibular nucleus. Relief of tremor has been maintained for as long as six months—the duration of the study, so far. Further experience is required in order to evaluate the clinical significance of these results. However, because of their physiologic significance, this preliminary report is made at the present time.

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Abstracts of Current Literature

THROMBOSIS OF THE MAJOR PULMONARY ARTERIES.

Amos, J. A. S. *Brit. M. J.* **2:** 659 (Sept. 13) 1958.

Thrombosis of the major pulmonary arteries is being recognized more frequently as a cause of clinical deterioration in a wide variety of predisposing illnesses. Nineteen cases are presented in which the thrombosis was confirmed at necropsy. They illustrate the variety of predisposing illnesses, the varying factors in pathogenesis, and the types of clinical illness that result. Fourteen of the patients were over age 50 at the time of death. There were 8 cases of the postembolic type (Group I) and 9 of autochthonous thrombosis (Group II). Chronic heart disease and emphysema were found in the latter. In the remaining 2 patients, the appearance of the thrombi suggested that they had formed terminally. Group I patients had a history of recurring episodes of clinical pulmonary embolism, and those in Group II had a history of increasing cor pulmonale which was often acute. The findings support the observation that the right artery is more frequently affected than the left. The condition may be suspected 1) when there is a history of venous thrombosis of the legs followed at various intervals, even years, by cardiorespiratory symptoms, 2) when there is unexplained deterioration in any of the known predisposing cardiac or respiratory illnesses (autochthonous thrombi are particularly likely to occur when local vascular disease is severe), and 3) when there are changes in physical signs, *e.g.*, changing heart signs, attacks of epigastric pain, and attacks of syncope. The characteristic radiologic alterations include right-sided enlargement of the heart, dilatation of the pulmonary artery proximal to the obstruction with alteration of the vessel contour, and increasing translucency of the lung fields distal to the obstruction. A change to right axis deviation from pre-existing left axis deviation may be detected by the electrocardiogram. The most frequent clinical course is that of repeated embolic episodes or of overwhelming acute cor pulmonale. Slowly progressive chronic cor pulmonale was seen in only 1 patient in this series.

ATURBAN (PHENGLUTARIMID), EIN NEUES BEHANDLUNGSMITTEL BEI PARKINSONISMUS. VERGLEICHENDE UNTERSUCHUNGEN ZUR BEHANDLUNG DES PARKINSONISMUS. (ATURBANE (PHENYLGLUTARIMIDE), A NEW AGENT FOR THE TREATMENT OF PARKINSONISM. INVESTIGATIONS IN THE MANAGEMENT OF PARKINSONISM).

Battegay, R. *Schweiz. med. Wchnschr.* **88:** 740, 1958; through Ciba Literature Review **3:** 278, 1958.

Sixty-three patients with Parkinson's syndrome of widely varying origin—such as drug-induced or arteriosclerotic parkinsonism, parkinsonism due to toxic causes, postencephalitic parkinsonism, or status post-infantile spastic diplegia—were treated with Aturbane (phenylglutarimide). Aturbane is a potent parasympatholytic agent with a mode of action similar to that of atropine, but with far lower toxicity. The dosage as a rule was 2.5 mg. three times daily, increased, if necessary, to 5 mg. three times daily. If side-effects occurred, the dosage was reduced to 1.25 mg. three times daily. The duration of treatment varied from a few weeks to several months. A positive response was observed usually after only one day. The therapeutic results were very satisfactory. The cases of parkinsonism caused by neuroplegic drugs responded particularly well, but even in parkinsonism of different origin Aturbane usually produced good results. Among the various symptoms, muscular rigidity and tremor improved most, but autonomic nervous and psychic changes were somewhat more difficult to control. Side-effects of a harmless type,

such as drowsiness, restlessness, giddiness and dryness of the mouth occurred only 6 times in the total of 63 cases. Serious complications or pathologic blood counts or urinary findings were not observed.

HYPERSENSITIVITY MYOCARDITIS OCCURRING WITH SULFAMETHOXYPYRIDAZINE THERAPY.

Blanchard, A. J., and Mertens, G. A. *Canad. M. A. J.* **79:** 627 (Oct. 15) 1958.

Three cases are reported of acute interstitial myocarditis found at necropsy and believed to be allergic in nature. In 2 instances the changes were so severe that they were assumed to be the cause of death. The condition was characterized by an accumulation of inflammatory cells throughout the heart muscle, with cardiac histiocytes and eosinophilic leukocytes predominating. These cells, scattered through the interstitial network of the myocardium, appeared to have a predilection for the perivascular regions. There was no associated vasculitis. All 3 patients were elderly men with urinary-tract infections treated with sulfamethoxypyridazine (Kynex, 0.5 Gm. two to three times daily). They were hospitalized for different reasons and no other parts of their therapy had been identical. Since the myocarditis was of a type seen in drug-induced hypersensitivity reactions, it was concluded to be a reaction to sulfamethoxypyridazine.

UNTERSUCHUNGEN ÜBER DIE WIRKUNG VON SYNTHETISCHEM HYPERTENSIN II AUF BLUTDRUCK, ATMUNG UND EXTREMITÄTENDURCHBLUTUNG DES MENSCHEN (INVESTIGATIONS OF THE ACTION OF SYNTHETIC HYPERTENSIN II ON BLOOD PRESSURE, RESPIRATION, AND BLOOD FLOW IN THE EXTREMITIES OF MAN).

Bock, K. D.; Krecke, H.-J., and Kuhn, H. M. *Klin. Wchnschr.* **36:** 254, 1958; through Ciba Literature Review **3:** 262, 1958.

The part played by the polypeptides, hypertensin I and II, as constituents of the so-called renin-hypertensin system—for instance, in the regulation of blood pressure—has not yet been fully elucidated. Now that the substances have been synthesized, it has become possible to study their properties more closely. Synthetic hypertensin II was administered intra-arterially and intravenously in doses of 0.01 to 10 gamma to healthy test subjects and the arterial blood pressure (measured in the blood), pulse rate, blood flow in the muscles and skin, and respiration were recorded simultaneously and continuously. When given intravenously in a single injection, hypertensin II caused a rise in blood pressure which commenced promptly, subsided rapidly, and was accompanied by bradycardia. Intravenous drip infusion raised the blood pressure to an elevated level, in keeping with the dose. The intra-arterial administration of hypertensin led to local constriction in the vessels of the skin and muscles of the extremities, but when the substance was administered intravenously a slight increase in blood flow, with negative pressure, occurred in muscle. The pressor effect of hypertensin II is appreciably more pronounced and sustained than that of noradrenaline. The rise in blood pressure produced by hypertensin is due to an increase in peripheral total resistance. Quantitatively, the extent to which the partial resistances of the circulation are involved in this effect is not the same as with noradrenaline. Vasoconstriction in the splanchnic region probably plays an essential part in the hypertensin effect. Respiration and basal metabolism are not demonstrably affected by hypertensin.

IL PUNTATO STERNALE NEGLI ULTRAOTTANTENNI. (STERNAL PUNCTURE IN PATIENTS OVER 80 YEARS OF AGE).

Cuzzato, E. *Gior. Gerontol.* **4:** 533, 1956, #11; through Excerpta Medica (Gerontol. & Geriatrics) **1:** 6, 1958.

The myelogram showed no substantial differences from that of adult subjects, notwithstanding the fact that the senile bone marrow undergoes a process of myeloid sclerosis.

The qualitatively normal function of the bone marrow of subjects over 80 years of age is derived from the fact that there remain islands of functioning marrow which escape fibro-adipose transformation and maintain sufficient cytoformative equilibrium, probably also due to the fact that the organism makes smaller demands.

LA DELTA-CORTISONE DANS LE TRAITEMENT DE L'INFARCTUS DU MYOCARDE. PREMIERS RESULTATS. (PREDNISONE IN THE TREATMENT OF MYOCARDIAL INFARCTION. PRELIMINARY RESULTS).

Giraud, G. *Med. et Hyg.* **16:** 281, 1958; through Ciba Literature Review **3:** 271, 1958.

Prednisone is suitable as an adjuvant in certain forms of myocardial infarction. This hormone is particularly indicated in the acute phase of the infarction when the inflammatory reaction is strongly marked. The response is the more striking, the higher the patient's fever. In these acute cases, a beneficial effect is soon observed on body temperature, disturbances of cardiac rhythm, general condition, and tissue metabolism. Once the acute phase has subsided, symptoms similar to those of humeroscapular periarthritis or shoulder-hand syndrome constitute a further indication for prednisone. Complete recovery from these complications can be achieved relatively quickly, provided treatment is initiated early. Precordial nonanginal thoracic pain is also favorably affected. When the infarction is accompanied by little fever and no symptoms of shock, classic methods of treatment without prednisone are sufficient. This study comprised 13 patients, only 2 of whom died. Prednisone was administered in daily dosages of 10 to 30 mg. for a period of six to twelve days. Analgesics, neuroplegics, and vasopressor agents were given concomitantly. The risk of a thrombo-embolism can be countered by administering anticoagulants. It can be inferred from animal experiments that, when used in the dosage stated, prednisone does not delay scar formation in myocardial lesions.

SENILE CONFUSION AND THE BLOOD SUGAR LEVEL.

Helps, E. P. W. *Lancet* **1:** 138, 1957; through Excerpta Medica (Gerontol. & Geriatrics) **1:** 32, 1958.

The occasional discrepancy between biochemical and clinical findings in hypoglycemia of elderly diabetic patients with cerebral arteriosclerosis is considered. Five case records are presented, in 3 of which acute episodes illustrate this point. In 4 cases, insidious mental deterioration appeared to have been arrested or reversed when hyperglycemia was deliberately permitted. Possible mechanisms are discussed. It is suggested that in the elderly diabetic patient with arteriosclerosis and consequently reduced blood flow, cerebral metabolism may become adapted to a supply of glucose in higher concentration than normal. Such supply may permit a higher level of metabolism than the reduced cerebral blood flow (oxygen supply) could otherwise support. Application of this principle to the management of nondiabetic elderly arteriosclerotic patients is discussed. A preliminary report of encouraging results obtained in such patients with senile confusion is given.

REFRACTORY EDEMA TREATED WITH CALCIUM CHLORIDE IN COMBINATION WITH MERCURIAL DIURETICS.

Hollister, J. M.; Lubash, G. D.; Cohen, B. D.; Braveman, W. S.; Rubin, A. L., and Luckey, E. H. *Am. Heart J.* **56:** 629 (Oct.) 1958.

In each of 12 patients with refractory edema, the creation of hyperchloremic acidosis through the administration of oral calcium chloride solution alone or in combination with acetazoleamide re-established responsiveness to a mercurial diuretic. Seven patients had Laennec's cirrhosis with pronounced liver dysfunction. Five patients had congestive heart failure, and in 2 of these there was laboratory evidence of liver dysfunction. Two case reports illustrate the response and lack of untoward effects in patients with liver disease.

Calcium chloride is considered a safe and effective substitute for ammonium chloride as a source of chloride in this regimen. Hyperchloremia and acidosis are achieved more readily when acetazoleamide is administered concomitantly with the chloride. The dosages were 750 mg. of acetazoleamide daily in one dose and 10 cc. of a 25 per cent solution of calcium chloride four times daily (10 Gm.). Frequent clinical and laboratory observations are essential in order not to extend the regimen to the point of symptomatic acidosis. The plasma pH or carbon-dioxide combining power and urinary chloride concentration should be determined daily. The former provides a guide to the degree of acidosis, and the latter to the amount of chloride presented to the renal tubules. When the urinary chloride concentration rises sharply, a response to mercurial diuretics may be expected. Acetazoleamide should be discontinued twenty-four hours prior to the administration of a mercurial agent.

DIE KLIMAKTERISCHE MYOPATHIE. (MENOPAUSAL MUSCULAR DYSTROPHY).

Kaeser, H. E. *Schweiz. med. Wchnschr.* **88:** 849 (Aug. 30) 1958.

Three typical and 2 probable cases of menopausal muscular dystrophy are presented. The results of biopsy, endocrinologic, electromyographic, and repeated transaminase examinations are given special attention. During the active phase of myopathy, glutamic oxaloacetic transaminase activity is increased. With prednisone, an impressive and lasting clinical improvement could be observed, in 1 case with normalization of transaminase activity. There is no final evidence as to whether menopausal muscular dystrophy is related to a myopathy or a chronic polymyositis. (From author's summary.)

HIRNATROPHISCHE PROZESSE DES HÖHEREN ALTERS. (CEREBRAL ATROPHY LESIONS IN ADVANCED AGE).

Kraemer, R. *Nervenarzt* **27:** 152, 1956, ✱4; through Excerpta Medica (Gerontol. & Geriatrics) **1:** 29, 1958.

On the basis of a survey of 73 patients, an attempt is made to distinguish between certain groups of cerebral atrophy lesions in old people. A rough division is made between primary cerebral atrophy (Pick's and Alzheimer's disease, senile-involutive lesions) and secondary cerebral atrophy (vasal, edema-necrotic, traumatic lesions), and between single and combined lesions. In all cases, the clinical symptoms and the effect of therapy are dependent on the individual tolerance limit and also on the extent and intensity of the parenchymatous atrophy. The diagnosis should rely only upon the hydrocephalus demonstrated by pneumoencephalography. The not infrequent discrepancy between the nature and degree of atrophy and the clinical picture induced the author to use the expressions of compensated and decompensated hydrocephalus. The treatise is a critical survey of this increasingly important problem.

EXSUDATIVE PLEURITIS IM ALTER. (EXUDATIVE PLEURISY IN OLD AGE).

Kutschera, W., and Bosina, E. *Wien. med. Wchnschr.* **107:** 497, 1957, ✱24; through Excerpta Medica (Gerontol. & Geriatrics) **1:** 26, 1958.

The theory that exudative pleurisy is mostly of tuberculous genesis holds true only for the lower ages. In 150 patients treated in the hospital who were over 50 years of age and showed exudative pleurisy as a main or secondary finding, the basic disease was pneumonia (38 per cent), carcinoma (3 per cent), pulmonary infarction (12 per cent), or tuberculosis (only 7 per cent). Parapneumonic exudates thus are of primary importance. In carcinoma patients, males predominated with 85 per cent bronchial carcinomas. A total of 59 patients were subjected to necropsy. Among them were 7 tuberculous patients with exudative pleurisy whose basic disease always was miliary tuberculosis with dissemination into the pleura, peritoneum and pericardium. The other patients showed mainly exudative pleurisy with severe cardiac decompensation, myocardial infarction, or multiple small pulmonary infarctions. So-called "rheumatic pleurisy" was not observed.

THE USE OF PHENMETRAZINE HYDROCHLORIDE (PRELUDIN) IN THE OBESE DIABETIC.
Leith, W., and Beck, J. C. *Canad. M.A.J.* **79:** 897 (Dec. 1) 1958.

Twenty obese diabetic patients between the ages of 41 and 81 years were followed for two to six months, during which therapy consisted of regular dietary control, insulin when indicated, and 25 mg. of phenmetrazine hydrochloride (Preludin) three times daily or a placebo given alternately for one month at a time. These patients had been followed for some time previously without satisfactory reduction in weight. Fifteen patients showed a substantial weight loss while receiving phenmetrazine. The drug did not significantly alter insulin requirements. A hyperglycemic effect occurred in only 1 case. In 5 patients, there was a fall in the blood sugar level while taking the medication. One new diabetic patient received phenmetrazine but no insulin. Her blood sugar level fell rapidly to normal as her weight decreased, and then a normal level persisted. It was concluded that phenmetrazine is a satisfactory agent for the long-term management of obese diabetic patients.

STUDIES OF ADRENAL CORTICAL FUNCTION IN THREE CASES OF CARCINOMA.
Lockwood, C. H. *Canad. M. A. J.* **79:** 728 (Nov. 1) 1958.

Three cases are reported of adrenocortical hyperfunction associated with carcinoma of the breast and carcinoma of the lung, and 1 case of primary adrenocortical carcinoma. They illustrate the variable clinical manifestations of adrenocortical hyperfunction. The significance of the association with carcinoma in these cases is unknown. Patient 1 had the classic physical characteristics of Cushing's syndrome. Carcinoma in the adrenal gland was wrongly regarded as a primary adrenal carcinoma. The excretion of 17-ketosteroids was elevated but less than is usual in the case of primary adrenocortical carcinoma. Masculinization was evident. An aldosterone effect was present intermittently. Hypokaliemia was found on several determinations. Death occurred from respiratory failure. Necropsy revealed infiltrating duct carcinoma of the breast with metastases to the lung, pleura and liver, but no tumor of the adrenal. In Patient 2, a small bronchogenic carcinoma with widespread metastases was unsuspected. The patient presented with hypotension and hypokaliemia. Increased urinary excretion of glucocorticoids, aldosterone and ketosteroids was found. The aldosterone effect predominated clinically and there was no evidence of glucocorticoid or androgen excess. In Patient 3, with a large mass of malignant adrenocortical cells, there were no physical or routine laboratory findings to suggest an endocrine abnormality prior to operation. A large mass in the upper abdomen was detected by intravenous pyelography. Examination of the surgical specimen established the presence of an adrenocortical tumor. Upon recurrence, the tumor was found to be producing mainly androgenic hormone. After ACTH therapy, the total urinary glucocorticoids were slightly above the normal level, and urinary 17-ketosteroids were elevated.

DETECTION OF ANTIGENS IN SERA OF PATIENTS WITH NEOPLASTIC DISEASE BY SCHULTZ-DALE TEST. ITS POSSIBLE USE AS A SCREENING PROCEDURE FOR TUMOURS.
Makari, J. G. *Brit. M. J.* **2:** 358 (Aug. 9) 1958.

By using antigens of smaller particle size than formerly in the Schultz-Dale test, it is possible to detect antigenic components in serum that are common to patients with various types of neoplastic disease. This procedure can be used as a screening test, and the original method will serve as a specific diagnostic test for carcinoma. The modified test accurately diagnosed a high percentage among 262 carcinomas, 130 malignant tumors, and 35 benign tumors. A positive result was obtained in 80 per cent of 59 precancerous lesions and suspected tumors. False positive results were obtained in 12.5 per cent of serum specimens from 80 healthy donors and in 12.6 per cent of 704 normal serum specimens from a blood bank. Preliminary studies indicate that the Schultz-Dale test may be helpful in studying the antigenic relations between various tumors.

SULL'IMPIEGO DELL'ATP IN ALCUNE MALATTIE NEUROPSICHICHE DELL'ETA SENILE. OSSERVAZIONI CLINICHE ED ELETTROENCEFALOGRAFICHE. (THE USE OF ATP IN SOME NERVOUS AND PSYCHIC DISEASES OF THE AGED. CLINICAL AND ELECTROENCEPHALOGRAPHIC OBSERVATIONS.)

Mars, G.; Morpurgo, M., and Severgnini, B. *Gior. gerontol.* **6:** 26, 1958.

Fourteen male patients ranging in age from 69 to 90 years and suffering from neuropsychic diseases of senility (5 cases of atherosclerotic dementia, 4 of senile dementia, 4 of atherosclerosis with focal manifestations, 1 of Parkinson's syndrome on an atherosclerotic basis) were treated with adenosine triphosphate (ATP) by the intramuscular injection twice daily of 30-mg. doses. The duration of treatment varied from twenty-two to forty days. The therapeutic activity of the drug was checked by means of clinical examination and through electroencephalographic tests. The electrocardiographic and electroencephalographic modifications produced by a single intravenous injection of 30 mg. of ATP were simultaneously studied in 3 cases. Registrations were made with a three-channel electrocardiograph suitably modified by means of the addition of an electronic amplifier. The improvement of the symptomatology, particularly of the confusional and depressive episodes, and of the electroencephalographic tracing (slowing down of the frequency, increased voltage, regularization of the morphology), observed in 8 cases, provide the basis for referring to possible mechanisms of action of the drug and for suggesting therapeutic attempts to treat with ATP some neuropsychic diseases of old age. (From authors' summary.)

IPRONIAZID (MARSILID) IN ANGINA PECTORIS.

Master, A. M. *Am. Heart J.* **56:** 570 (Oct.) 1958.

Seventy-four patients with severe angina pectoris were treated with iproniazid, beginning with 150 mg. daily, for one week to five months. In long experience with innumerable drugs for coronary disease, no other has approached the subjective relief attained with iproniazid. In more than half of the patients, that is, 41, iproniazid relieved the anginal syndrome completely or almost completely. Five of these patients were in "status anginosus." In 29 there was no relief of pain; 1 of these was a case of "status anginosus." Neither the resting electrocardiogram nor the Master "2-step" test result was altered during the course of treatment with iproniazid, indicating that the fundamental coronary disease was not changed, at least in this five-month period. The precise mechanism of the relief of pain by iproniazid is unknown. It can possibly be explained by cerebral stimulation, with uplift of mood, and increase of the pain threshold. There may be a direct effect on the autonomic nerve connections between the heart and the spinal cord and brain. The side-effects were mainly gastro-intestinal, genito-urinary and cardiovascular, the latter including dizziness, fall in arterial pressure, and syncope. Less common complications were evidences of cerebral stimulation, peripheral neuritis, dryness of the mouth, hepatitis and gain in weight. One case of hepatitis occurred, with subsequent recovery. Four patients noted significant gain in weight. The fall in blood pressure is probably a factor in syncope and in episodes of acute coronary insufficiency; it may possibly be a factor in the precipitation of coronary occlusion. The physical overactivity associated with euphoria, excitement, and the loss of pain, may cause coronary insufficiency. The patient receiving iproniazid should be supervised very closely. Blood pressure should be measured in the standing position. On the other hand, nitroglycerin should never be taken by the patient except in the sitting or recumbent position. In view of the numerous side-effects, some of which are dangerous, iproniazid should be studied further only in hospitals and by research teams. It is to be hoped that diligent investigators will continue to seek an analog of iproniazid which will relieve angina, and will not be dangerous. (From author's summary and conclusion.)

THE RELATIONSHIP TO RHEUMATOID ARTHRITIS OF ITS SO-CALLED VARIANTS.

McEwen, C.; Ziff, M.; Carmel, P.; DiTata, D., and Tanner, M. *Arth. & Rheum.* **1:** 481 (Dec.) 1958.

A number of joint diseases which have been thought to be special forms or variants of rheumatoid arthritis are discussed, and the clinical, pathologic and radiologic features which support such a relationship and those which raise doubts are briefly reviewed. Sheep erythrocyte agglutination tests were performed by the inhibition technic on the euglobulin fraction of sera from patients with each kind of disease. On the basis of the data obtained, it is concluded that Still's disease represents true juvenile rheumatoid arthritis. Ankylosing spondylitis, Reiter's disease, arthritis accompanying psoriasis, and arthritis accompanying ulcerative colitis, on the other hand, are judged to be distinct from rheumatoid arthritis.

THE CHEMOTHERAPEUTIC EFFECTS AND COMPLICATIONS OF ACTINOMYCIN D IN PATIENTS WITH ADVANCED CANCER.

Moore, G. E.; DiPaolo, J. A., and Kondo, T. *Cancer* **11:** 1204 (Nov.–Dec.) 1958.

Actinomycin D was given intravenously to 67 patients with advanced carcinoma in total dosages of 50 or 75 gamma per kilogram of body weight in fractional doses. Transitory regressions were obtained in 3 of 16 patients with carcinoma of the breast, 3 of 5 with lymphosarcoma, 2 of 12 with carcinoma of the gastro-intestinal tract, 1 of 8 with malignant melanoma, and 4 of 34 with miscellaneous adenocarcinomas. There was no apparent difference in response according to dosage. The evaluation of a response was based upon direct or indirect measurements of the diameter of metastatic masses. Nine remissions lasted less than one month, and 3 for longer than a month. Tumor growth appeared to be accelerated both following regression and in the absence of a response in some instances. The peripheral blood in some patients was cleared of tumor cells after therapy during which no reduction in tumor size was noted. In a few patients given maintenance therapy after initial evaluation, the tumor did not regress. There was some evidence of tolerance to the drug. Toxic reactions included nausea and vomiting, anorexia, diarrhea, severe ulceration of the mouth and tongue, and to a lesser extent, acne, alopecia and mild hemorrhagic colitis. Thrombocytopenia and leukopenia were seen in 42 and 30 per cent, respectively, of patients given a complete course of therapy. The response to actinomycin D was dramatic but these studies are not believed to indicate that the drug will be of clinical value in the treatment of advanced carcinoma.

EXPERIMENTS IN IMMUNITY IN CANCER.

Murray, G. *Canad. M. A. J.* **79:** 249 (Aug. 15) 1958.

Studies on the production and use of an anti-cancer serum support the view that cancer is caused by something against which, either actively or passively, antibodies can be made and host resistance to cancer improved. Human cancer tissue emulsified in saline was injected into horses. Following a series of immunizing injections, blood was drawn and fractionated to remove the globulin fraction which would contain the antibodies. The evidence showed that antibodies actually had been produced. The serum was used only in patients with massive recurrent carcinoma who had undergone all advised methods of treatment by operation, radiation and hormones, or who had received these treatments without benefit. All had multiple and distant metastases. Included were cases of massive recurrence in the skin and chest wall following mastectomy in which no further radiation was justified, intracranial metastases, mediastinal infiltration, multiple pulmonary metastases, and pulmonary and pleural metastases with massive pleural effusion. Involvement of the liver was accepted as an absolute contraindication to use of the serum. Following skin sensitization tests, the serum was injected intravenously in 0.5-cc. amounts and the

dose doubled daily until a 20-cc. dose had been reached. Injections were continued until 300 cc. had been administered in three to four weeks' time on the average. Two hundred and thirty-three patients were treated, of whom 91 had received the full dosage at the time of reporting. Of these, 62 had carcinoma of the breast. Thirty-three patients had metastatic gastric carcinoma, and 27 had metastatic carcinoma of the colon. The serum produced no cures but many patients experienced satisfactory palliation both from their own standpoint and from that of the observer. Patients with severe bone pain were likely to obtain some, and often complete relief of pain. Some osteolytic lesions became satisfactorily recalcified. Proof was lacking that any was cured, but the effect seemed to be as good as that from radiation therapy. Many patients in a terminal condition lived one, two, or three years after receiving the anti-cancer serum. The serum offers better palliation than other means of therapy. The relief of pain alone is sufficient to justify its use as a palliative measure.

STUDIO RADIO-STRATIGRAFICO SUL COMPORTAMENTO DELLE ARTICOLAZIONI SACRO-ILIACHE NELL'UOMO DI ETÀ SENILE. (A RADIO-STRATIGRAPHIC STUDY OF THE CHANGES OF THE SACROILIAC JOINT IN SENILE HUMAN BEINGS).

Mussa, L., and Tardy, A. *Reumatismo* **9:** 77, 1957; through Excerpta Medica (Gerontol. & Geriatrics) **1:** 53, 1958.

The sacro-iliac joints of 100 men older than 50 years were studied by frontal and oblique radiography and by stratigraphy, with the purpose of determining the frequency of ankylosis of this joint in senility. Partial or total mono- or bilateral ankylosis was observed in 31 of the subjects (three times in a group of 30 aged 50 to 59 years; eight times in a group of 30 aged between 60 and 69 years; and twenty times in a group of 40 aged 70 years or older). Only 1 subject exhibited bilateral total ankylosis of a radiologic aspect similar to that habitually seen in the terminal phase of sacroiliitis due to ankylosing spondylitis. In all subjects, the lumbo-sacral spine and the hip joints also were examined, but no particular relations were found between sacro-iliac ankylosis and the degree of development and the size of degenerative processes in the joints nearby. It seems that sacro-iliac bone fusion depends mainly on the senescence factor, since its frequency increases in direct proportion to age.

SUBDURAL HEMATOMA RELATED TO ANTICOAGULATION THERAPY.

Nathanson, M.; Cravioto, H., and Cohen, B. *Ann. Int. Med.* **49:** 1368 (Dec.) 1958.

Three cases are reported of subdural hematoma occurring in relation to anticoagulant therapy. In 1 patient, the hematoma was not suspected and found only at necropsy. The diagnosis was made radiographically in the other 2 patients, and the hematoma was removed successfully in one of them. When mental and neurologic signs develop during the course of anticoagulant therapy, the possibility of subdural hematoma should be considered. The possibility exists that "minor" trauma to the head during anticoagulant therapy may be an initiating factor.

THE EFFECT OF NICOTINIC ACID, PHENYL-ETHYL-ACETAMIDE, AND A COMBINATION OF BOTH DRUGS ON HYPERCHOLESTEROLEMIC DOGS AND HUMAN BEINGS.

Nava, A.; Comesana, F.; Lozano, E.; Fishleder, B. L., and Sodi-Pallares, D. *Am. Heart J.* **56:** 598 (Oct.) 1958.

The effect of nicotinic acid alone and in combination with phenyl-ethyl-acetamide on cholesterol levels in plasma was studied in dogs with induced hypercholesteremia and in arteriosclerotic patients with hypercholesteremia. In dogs, nicotinic acid in 100-mg. daily doses had a rapid hypocholesteremic effect which was maintained during administration

of the drug. The plasma cholesterol levels started to rise the day following its discontinuation and reached the high levels of the post-control period on the second day. Phenyl-ethyl-acetamide in 400-mg. daily doses lowered the cholesterol levels in the 3 dogs studied but to a lesser extent than did nicotinic acid. The decrease, which was significant and sustained, began on the first day of treatment. When the drug was discontinued, the cholesterol level rose slowly beginning with the second day, but the levels were lower than those obtained in the second control period. The effect of these drugs in combination was greater than that of either one alone. The combination returned the cholesterol levels almost to control values in 5 dogs tested. The effect was sustained for two days after the combination was discontinued. The cholesterol levels remained as low as in the first control period before the hypercholesteremic diet was begun. Nicotinic acid in doses of 300 mg. daily produced, between the second and fourth weeks of administration, an average decrease of 35 per cent in the serum cholesterol levels of 30 patients with coronary, cerebral, or peripheral arteriosclerosis in the majority of whom the initial values were above 300 mg. per 100 cc. The effect was more pronounced in those patients with the higher cholesterol levels. Within two to four weeks after nicotinic acid had been withdrawn, the cholesterol levels returned almost to the control values. Satisfactory results in man with daily dosages of 400 to 600 mg. of nicotinic acid make the dosages of 3 to 6 Gm. used by other investigators appear to have been excessive. In a preliminary study in 4 patients treated with a combination of 300 mg. of nicotinic acid with 2.4 Gm. of phenyl-ethyl-acetamide daily in fractional doses, the cholesterol values in patients with arteriosclerosis and hypercholesteremia were decreased. This investigation, which confirms the results of pharmacologic studies, will be extended.

TOXIC EFFECTS OF IPRONIAZID IN A PATIENT WITH ANGINA.

Papp, C., and Benaim, S. *Brit. M. J.* **2:** 1070 (Nov. 1) 1958.

The frequency of attacks of decubital angina in a female patient was reduced upon treatment with iproniazid in a dosage of 50 mg. two to three times daily. Pethidine was still needed occasionally for the relief of pain. During the fifth week of iproniazid treatment, the injections of pethidine were followed by signs of severe cerebral irritation and excitement which were controlled only by chlorpromazine. This reaction was caused either by the additive effects of the 2 drugs or because iproniazid interfered with the normal detoxification of pethidine in the liver. It is pointed out that patients with decubital angina require heavy sedation with morphine analogs and barbiturates. The potentiation of these drugs with iproniazid may give rise to toxic cerebral reactions. They should, therefore, be used with caution in patients receiving iproniazid.

UROPEPSIN AND 17-HYDROXYCORTICOID EXCRETION IN NORMAL SUBJECTS AND PATIENTS WITH PEPTIC ULCER DURING BOTH STATES OF ACTIVITY AND QUIESCENCE.

Sleisenger, M. H.; Lewis, C. M.; Lipkin, M., and Wierum, C. *Am. J. Med.* **25:** 395 (Sept.) 1958.

The 24-hour excretion of uropepsin was determined in normal subjects, and patients with gastric ulcer, active and inactive duodenal ulcer, and steroid ulcers; in all, 91 determinations in 70 subjects. In addition, the 24-hour urinary excretion of 17-hydroxycorticoids was determined in 48 of the patients. Significant differences were found in uropepsin excretion in the groups of patients with gastric ulcer and inactive duodenal ulcer when compared to the normal group. However, the standard deviation of the results within the groups was so large that any attempt at delineation of normal and abnormal ranges would be of minimal value. There was no significant difference between uropepsin values in patients with active duodenal ulcer and in normal subjects. In addition, there was no significant difference between uropepsin values in cases of duodenal ulcer during periods

of activity and during periods of quiescence. The excretion of 17-hydroxycorticoids remained within normal limits in patients with active and inactive ulcer, and in those in whom steroid ulcers had developed. A positive correlation of uropepsin and 17-hydroxycorticoids was obtained only in a small group of patients either with Cushing's syndrome or under treatment with ACTH; that is, uropepsin values were consistently elevated when there was increased 17-hydroxycorticoid output. This study demonstrated: 1) either that urinary uropepsin does not accurately reflect gastric secretory activity or that the intensity of gastric secretory activity bears no relationship to activation of duodenal ulcer; 2) that there is no evidence for increased adrenocortical activity in patients with idiopathic duodenal ulcer, particularly during periods of activation; and 3) that when adrenocortical hyperactivity, as reflected by urinary 17-hydroxycorticoid excretion does exist, urinary uropepsin is predictably elevated. (From authors' summary.)

"DURAFOAM"—A NEW MATERIAL FOR REST SPLINTS IN THE PREVENTION OF DEFORMITY IN THE CHRONIC RHEUMATIC DISEASES.

Swanson, J. N. *Canad. M. A. J.* **79:** 638 (Oct. 15) 1958.

DuraFoam splints can be used to prevent some of the disability in rheumatoid arthritis, by resting a swollen joint and avoiding damage to the muscle. DuraFoam splinting is accomplished by the use of a rapid-setting plastic foam inside a plastic envelope which is cut according to a predesigned shape and applied to the body. A quick final hardening results in a contour-fitting, light splint. The envelope has a resilient coating on the side applied to the body, which acts as a buffer and pressure padding. If a skin-tight fitting is necessary, the DuraFoam can be applied without the lining. The splint is held in place with an ordinary tensor bandage until it has hardened. The splint can then be fastened with an elastic or plastic band. The advantages of DuraFoam are as follows: light; comfortable; snug-fitting; not messy (no protective clothing required); stronger by weight than other plastic; rapidly setting, yet easily molded without cracking; capable of being remodelled if heated; washable, waterproof and buoyant; can be made under water; unaffected by oil, ointment, alcohol or secretions; not flammable; transparent to x-rays; insulated and thus cool; neither hot nor clammy; shock-resistant and resilient; will not crumble; nontoxic; allergy-free; attractively colored; and inexpensive.

ERRATUM

In the article entitled "Treatment of Low-Resistance Syndromes" by C. B. Favour (*J. Am. Geriatrics Soc.* **7:** 184–192 (Feb.) 1959) the first word in the second line of the second paragraph should be "vertebrates" instead of "invertebrates."